Comparative Effectiveness of Pemetrexed-platinum Doublet Chemotherapy With or Without Bevacizumab as First-line Therapy for Treatment-naive Patients With Advanced Nonsquamous Non−small-cell Lung Cancer in China

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ABSTRACT

Purpose: Bevacizumab plus platinum-based doublet chemotherapy is recommended by the National Comprehensive Cancer Network as a category 1 regimen and is widely used in patients with advanced nonsquamous non−small-cell lung cancer (NS-NSCLC). In China, a common first-line chemotherapy for NS-NSCLC is the pemetrexed-platinum doublet regimen (Pem-Pt). However, limited evaluation exists to show the effectiveness of the Pem-Pt + bevacizumab (Bev) regimen in advanced NS-NSCLC. This study describes the treatment patterns, effectiveness, and safety profile of Pem-Pt + Bev in patients with NS-NSCLC in China in clinical practice.

Methods: Data from eligible patients with advanced NS-NSCLC who received Pem-Pt with (136 patients) or without (97 patients) bevacizumab from January 2012 to March 2017 were retrospectively evaluated. The effectiveness outcomes included the assessment of progression-free survival (PFS) and objective response rate (ORR) in the overall population, the percentage of patients with pleural effusion or brain metastasis, as well as the percentage of patients receiving maintenance therapy. Moreover, the intracranial remission rate in patients with brain metastasis was estimated. Finally, the adverse events with the 2 treatments were addressed.

Findings: Compared with the Pem-Pt regimen, the Pem-Pt + Bev regimen was associated with a significantly longer median PFS and a higher ORR in the overall population ($P = 0.0002$). An improvement in ORR was observed in Pem-Pt + Bev−treated patients with brain metastasis ($P = 0.0045$). Moreover, patients receiving Pem-Pt + Bev and maintenance therapy not only showed a longer median PFS than that in those whose treatment was interrupted after induction but also a longer median PFS than that in patients who received Pem-Pt and maintenance therapy. The safety profile was acceptable in all groups, with no observations of hypertension, proteinuria, severe bleeding (1 case of grade I epistaxis was reported with Pem-Pt + Bev), or any unexpected findings reported.

Implications: These results from clinical practice further support the concept that pemetrexed-platinum doublet plus bevacizumab could be an effective and tolerable regimen in patients with advanced NS-NSCLC in China. (*Clin Ther*. 2019;41:518−529)

Keywords: bevacizumab, brain metastasis, maintenance therapy, nonsquamous non−small-cell lung

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cancer (NS-NSCLC), pemetrexed-platinum doublet, pleural effusion.

INTRODUCTION

Lung cancer is the leading cause of cancer death and the most commonly diagnosed cancer type in China. Moreover, the increasing prevalence of lung cancer in China is higher than that in Western countries.[1] An estimation of 733,000 new cases per year of lung cancer in China has been reported,[2] and the World Health Organization estimates that by the year 2025, >1 million people per year would be diagnosed with lung cancer in China.[3]

The epidemic of lung cancer is a major health issue confronting both developed and developing countries, given the high mortality rates worldwide. There are 2 major types: non−small-cell lung cancer (NSCLC), which accounts for 85%−90% of all cases of lung cancer,[4] and small-cell lung cancer (SCLC), which grows and spreads in different ways and therefore is treated using different procedures. In addition, NSCLC can be classified into 3 subtypes: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.[4] Treatment options for lung cancer vary depending on the cancer type, stage, tumor size, and localized position/metastasis, in addition to the overall physical health of the patient. Moreover, the survival rate in patients with lung cancer is highly related to the stage of lung cancer at which a patient is diagnosed. Patients with early-stage or localized NSCLC may be successfully treated by surgery. Up to 70% of patients survive for at least 5 years after diagnosis if treated at this stage, with some patients achieving lifelong remission. Unfortunately, because of the nonspecific nature of lung cancer symptoms (eg, cough), most patients with lung cancer are not diagnosed until the cancer has progressed to the advanced stage (49% of lung cancers in China are detected with metastasis at first diagnosis,[5] versus 29% in Japan[6] and 38% in the United States[7]), with only 20% being eligible for surgical treatment with curative intent.[1]

Conventional chemotherapy combinations are the recommended regimen in patients with NSCLC without alteration in driver oncogene (ie, *EGFR/ALK/ROS1*).[8] For nonsquamous cell−type (NS)−NSCLC, platinum-based 2-drug regimens are the first-line choice.[9,10] In second-line settings, a combination of docetaxel and pemetrexed is used as a single agent.[9,10] However, the efficacy of platinum-based doublet in NSCLC is limited, with a 5-year survival rate of 10% to 15% and a median survival of ~8 to 10 months.[11] Vascular endothelial growth factor (VEGF) is an essential factor in tumor-associated growth and angiogenesis,[12] and a therapeutic intervention targeting the VEGF pathway has become a mainstay of cancer therapy.[13] A humanized monoclonal antibody, bevacizumab, has been approved as a VEGF antagonist by U S Food and Drug Administration (FDA) for the treatment of several kinds of cancers.[13] Since 2004, several studies have demonstrated that a platinum-based regimen plus bevacizumab could prolong progression-free survival (PFS) in patients with advanced NS-NSCLC.[14] This regimen is therefore recommended by the National Comprehensive Cancer Network as a category 1 regimen and is widely used for the treatment of advanced NS-NSCLC.[15] Moreover, based on a China-specific Phase III trial (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),[16] the Food and Drug Administration of China approved carboplatin-paclitaxel plus bevacizumab as first-line therapy for metastatic NS-NSCLC in 2015.

With an aim to investigate the effectiveness and tolerability of bevacizumab, bevacizumab-specific observational cohort studies were conducted to explore clinical outcomes among broader populations, with patients receiving bevacizumab in treatment regimens in clinical practice. Among these studies, several have compared the regimen of paclitaxel-carboplatin plus bevacizumab and paclitaxel-carboplatin therapy in advanced NSCLC, with findings that support the clinical benefits of bevacizumab.[17,18] Moreover, a pemetrexed-platinum regimen has shown noninferior PFS but a better safety profile compared with a gemcitabine-platinum regimen in patients with NSCLC.[19] However, the evaluation of a pemetrexed-platinum plus bevacizumab (Pem-Pt + Bev) regimen in patients with advanced NS-NSCLC in China in a clinical practice setting is insufficient. In this retrospective study, clinical outcomes with the Pem-Pt + Bev regimen in patients with advanced NS-NSCLC

in China were collected and evaluated—in particular, the effectiveness of bevacizumab in patients with brain metastasis or pleural effusion. Outcomes in a subcohort of patients receiving Bev + Pem maintenance therapy were also analyzed and are discussed in this article.

PATIENTS AND METHODS

Patient Enrollment

This observational, single-center study captured clinical data from patients with advanced NS-NSCLC in China who received first-line Pem-Pt ± Bev between January 2012 and March 2017. This study was without any statistical assumptions or hypothesis testing. Therefore, no statistical hypothesis-based sample size was calculated. The data from eligible patients were collected according to the eligibility criteria at Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China. The eligible inclusion criteria were limited to: (1) the provision of written informed consent; (2) adult age (≥18 years); (3) new diagnosis of local advanced or metastatic NS-NSCLC (ie, Stage IIIB-IV according to the 7th edition of the International Association for the Study of Lung Cancer staging system, and confirmed by histologic or cytologic examination); (4) Eastern Cooperative Oncology Group performance status (ECOG PS) scale score of 0 to 2; (5) receipt of first-line Pem-Pt ± Bev; (6) good compliance and completion of at least 2 treatment cycles; and (7) completeness of full medical records. Exclusion criteria included pathologically confirmed SCLC, mixed SCLC, or early-stage NSCLC. A flowchart and analysis cohorts are presented in Figure 1.

This study was conducted in accordance with the ethics principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethics standards. Before study initiation, the study protocol was approved by the institutional ethics review board. Patients and physicians were required to provide written consent to release information before data collection.

Study Design

The primary effectiveness end point, PFS, was defined as the time from the initiation of treatment to objective tumor progression or death. Response was classified as complete response, partial response, stability of disease, and progressive disease, according to response evaluation criteria in solid tumors (RECIST 1.1; New Response Evaluation Criteria in Solid Tumors).[20] The objective response rate (ORR) was calculated as compete response + partial response.

Tolerability outcomes were measured by the prevalence of adverse events (AEs), which were evaluated according to the National Cancer Institute's Common Toxicity Criteria for Adverse Events version 4.03. Intracranial response in evaluable patients with brain metastasis was examined by magnetic resonance imaging or computed tomography, according to RECIST 1.1, and estimated by ORR.

Treatment Received

All patients received at least 2 cycles (21 days/cycle) of treatment, in which they were given pemetrexed (500 mg/m^2) plus platinum doublet chemotherapy (cisplatin 75 mg/m^2 or carboplatin at target AUC = 5), with or without bevacizumab (7.5 mg/kg). The effect was evaluated after 2 cycles. If the treatment was effective, it was continued for 4 to 6 cycles, followed by maintenance treatment until disease progression.

Data Collection

Patients' data, including the chief complaint, disease history, physical examination, imaging examinations, and biochemical laboratory tests, were collected and reviewed manually by physicians at the time of initial enrollment until at least 2 cycles of treatment had been completed or until disease progression, death, or study cutoff.

Statistical Analysis

Statistical analysis was performed by an experienced biostatistician after the completion of data collection and verification. Full demographic information and baseline characteristics of the patients were tabulated and analyzed by treatment group. The χ^2 test or Fisher exact test was used to identify significant differences in baseline characteristics between treatment groups. For categorical variables, both the number of patients and the percentage are shown. The Kaplan–Meier method and log-rank test were used to obtain and compare the survival curves of PFS between treatment groups. Multiple Cox regression was performed to estimate the impact of bevacizumab administration on PFS in both the overall population and in the subgroups after adjustment for confounding. Multivariate or

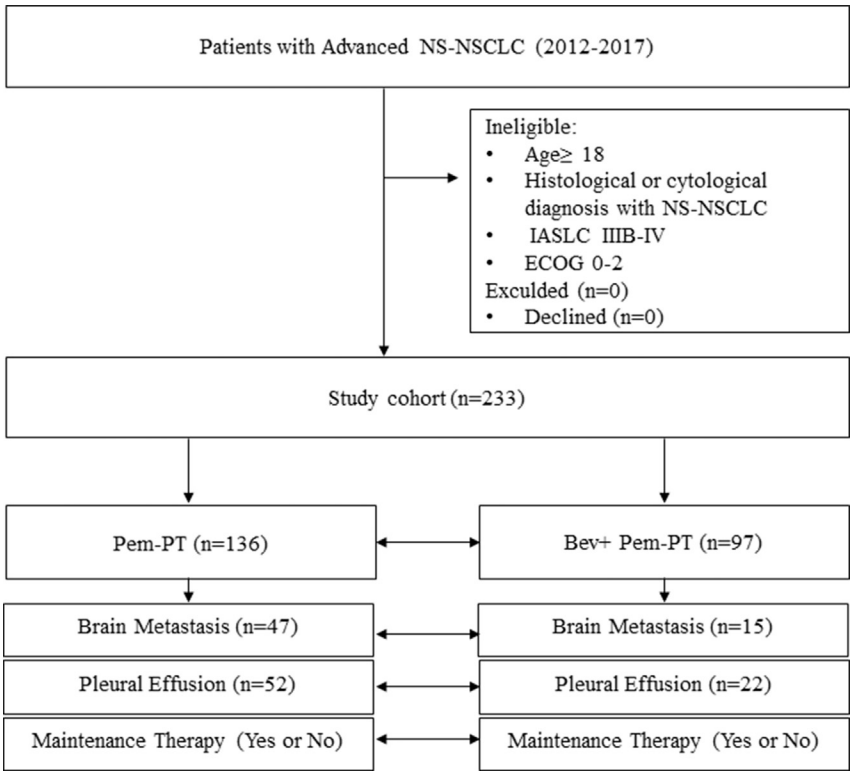

Figure 1. Study design. Bev = bevacizumab; ECOG = Eastern Cooperative Oncology Group performance status; IASLC = International Association for the Study of Lung Cancer stage; Pem-Pt = pemetrexed-platinum–based chemotherapy.

univariate logistic regression analyses were used to determine the associations between bevacizumab administration and ORR in the overall population as well as in patients with brain metastases. The difference in ORR between treatment groups was tested for significance using the χ^2 test. Unless specified, all statistical tests were 2-tailed and performed at the 5% significance level. All analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Baseline Characteristics and Patient Demographics

Data from 233 patients with advanced NS-NSCLC in China diagnosed with advanced NS-NSCLC between January 2012 and March 2017 and who met the selection criteria at our cancer center were reviewed for this study (Pem-Pt, n = 136; Pem-Pt + Bev, n = 97). Patients who received carboplatin, cisplatin, bevacizumab plus carboplatin, or bevacizumab plus cisplatin were included in the outcomes analysis; 22 additional patients who received "other" treatment with or without bevacizumab were included only in the baseline analyses (Figure 1 and Table I).

Although the patients were not randomized to treatment, patients' baseline characteristics were similar across several parameters in the treatment cohorts—age, sex, disease stage, ECOG PS, and epidermal growth factor receptor (*EGFR*) driver mutations (Table I). The overall study was composed of 146 (62.7%) male and 87 (37.3%) female patients, whose ages ranged from 17 to 81 years. Most of the patients were diagnosed at Stage IV and had an ECOG PS of 0 to 1.

Effectiveness Outcomes

In the overall population, the median PFS was significantly longer in the Pem-Pt + Bev group than in the Pem-Pt group (10.97 vs 6.67 months; $P = 0.0002$)

Table I. Baseline characteristics of the study population. Data are given as number (%) of patients.

Characteristic	Pem-Pt (n = 136)	Pem-Pt + Bev (n = 97)	*P*
Sex			0.5421[a]
Male	83 (61.03)	63 (64.95)	
Female	53 (38.97)	34 (35.05)	
Age group			0.5864[a]
<65 y	102 (75.00)	74 (76.29)	
65–74 y	30 (22.06)	18 (18.56)	
≥75 y	4 (2.94)	5 (5.15)	
IASLC			0.3101[a]
IIIB	9 (6.62)	10 (10.31)	
IV	127 (93.38)	87 (89.69)	
ECOG			0.4047[b]
0–1	132 (97.06)	96 (98.97)	
2	4 (2.94)	1 (1.03)	
EGFR mutation			0.2595[a]
Positive	42	38 (39.18)	
Negative	46 (33.82)	24 (24.74)	
Unknown	48 (35.29)	35 (36.08)	
Brain metastases			0.0011[a]
Yes	47 (34.56)	15 (15.46)	
No	89 (65.44)	82 (84.54)	
Pleural effusion			0.0119[a]
Yes	52 (38.24)	22 (22.68)	
No	84 (61.76)	75 (77.32)	
Chemotherapy			0.0059[a]
Carboplatin	47 (34.56)	54 (55.67)	
Cisplatin	77 (56.62)	37 (38.14)	
Others	12 (8.82)	6 (6.19)	

Bev = bevacizumab; ECOG = Eastern Cooperative Oncology Group performance status; IASLC = International Association for the Study of Lung Cancer stage; Pem-Pt = pemetrexed-platinum–based chemotherapy.
[a] χ^2 test.
[b] Fisher exact test.

(Figure 2 and Table II). Similarly, the ORR was improved in the Pem-Pt + Bev group (63.92% vs 20.74%; odds ratio = 7.63; 95% CI, 3.96–14.67; $P < 0.0001$) (Table II).

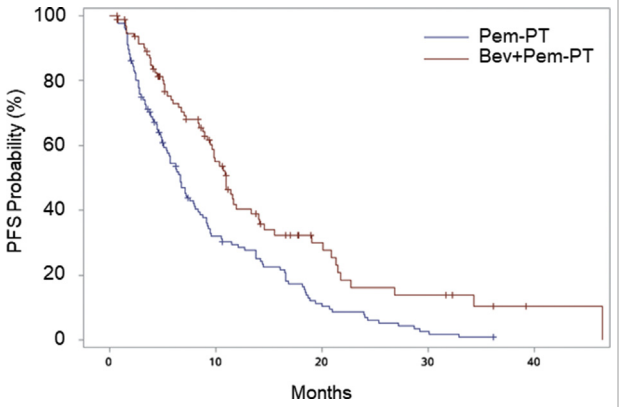

Figure 2. Progression-free survival (PFS) after treatment with pemetrexed-platinum–based chemotherapy (Pem-Pt) ± bevacizumab (Bev) in patients with NS-NSCLC.

The findings from all of the subgroup analyses likewise support a benefit in PFS in the Pem-Pt + Bev arm, as shown in the overall population. In the subgroup with brain metastasis, the median PFS in the Pem-Pt + Bev group was 9.79 months compared with 6.21 months in the Pem-Pt group (hazard ratio = 0.569; 95% CI, 0.282–1.147; $P = 0.115$) (Table III and Figure 3A). Consistently, intracranial remission in patients with brain metastasis was significantly improved in the Pem-Pt + Bev group, with a higher ORR (66.67% vs 22.22%; $P = 0.0045$) (Table IV). In patients diagnosed with pleural effusion, the median PFS was 9.66 months in the Pem-Pt + Bev group compared with 7.26 months in the Pem-Pt group (hazard ratio = 1.079; 95% CI, 0.566–2.055; $P = 0.8177$) (Table III and Figure 3B). Notably, the patients who chose to receive maintenance therapy after the induction of treatment with Pem-Pt + Bev had the most-extended PFS compared with patients receiving Pem-Pt + maintenance or Pem-Pt only (median, 10.97 vs 8.51 and 4.43 months, $P < 0.001$ respectively) (Figure 4).

Safety Profile

The prevalences of bevacizumab-associated serious AEs, such as hypertension, gastrointestinal perforations, arterial and venous thromboembolic events, hemoptysis, and hemorrhage,[18] were

Table II. Response after treatment with pemetrexed-platinum–based chemotherapy (Pem-Pt) ± bevacizumab (Bev) in patients with NS-NSCLC.

Parameter	Pem-Pt (n = 136)	Pem-Pt + Bev (n = 97)	*P*
Response type, no. (%)			<0.0001[a]
CR	0	0	
PR	28 (20.74)	62 (63.92)	
SD	79 (58.52)	28 (28.87)	
PD	28 (20.74)	7 (7.22)	
ORR (CR + PR), no. (%)	28 (20.74)	62 (63.92)	<0.0001[a]
OR (95% CI)	Ref.	7.63 (3.96–14.67)	<0.0001[b,c]
PFS, median, mo	6.67	10.97	0.0002[d]
HR (95% CI)	Ref.	0.58 (0.41–0.82)	0.0022[c,e]

CR = complete response; HR = hazard ratio; OR = odd ratio; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.
[a] χ^2 test.
[b] Multiple logistic regression.
[c] Variables adjusted in the model include: sex, age, stage, ECOG, *EGFR* status, brain metastases, pleural effusion, and chemotherapy.
[d] Log rank test.
[e] Multiple Cox regression.

Table III. Brain metastasis and pleural effusion in NS-NSCLC patients with PFS after treatment with pemetrexed-platinum–based chemotherapy (Pem-Pt) ± bevacizumab (Bev).

Parameter	*n*	PFS, median, mo	HR (95% CI) (ref. = Pem-Pt)	*P*[a]
Brain metastasis				
Yes	62		0.569 (0.282–1.147)	0.1150
Pem-Pt + Bev	15	9.79		
Pem-Pt	47	6.21		
No	171		0.544 (0.362–0.819)	0.0035
Pem-Pt + Bev	82	10.97		
Pem-Pt	89	7.26		
Pleural effusion				
Yes	74		1.079 (0.566–2.055)	0.8177
Pem-Pt + Bev	22	9.66		
Pem-Pt	52	7.26		
No	159		0.465 (0.308–0.702);	0.0003
Pem-Pt + Bev	75	11.40		
Pem-Pt	84	6.27		

PFS = progression-free survival; HR = hazard ratio.
[a] Multiple Cox regression, variables adjusted in the model include: sex, age, stage, Eastern Cooperative Oncology Group performance status, *EGFR* status, brain metastasis/pleural effusion, and chemotherapy.

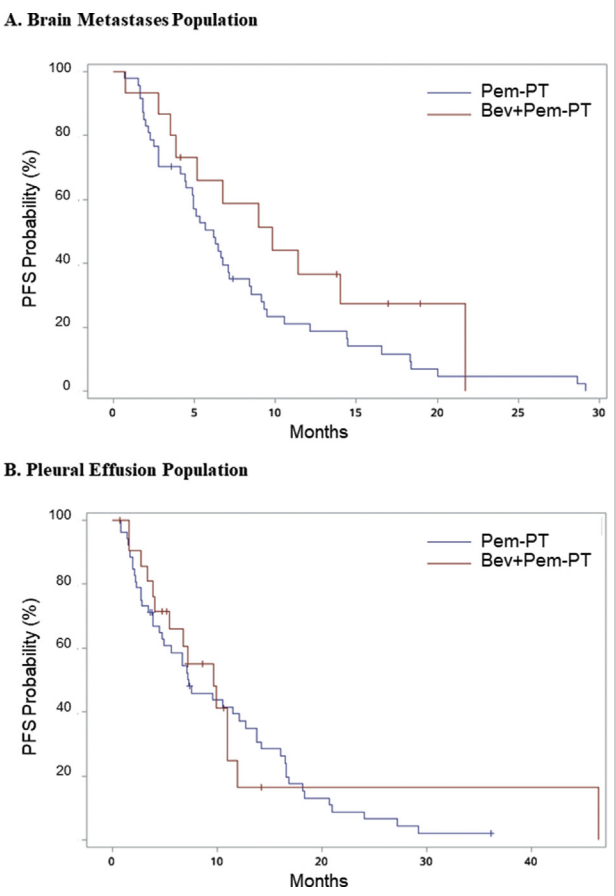

Figure 3. Brain metastasis (A) and pleural effusion (B) in NS-NSCLC patients with progression-free survival (PFS) after treatment with pemetrexed-platinum–based chemotherapy (Pem-Pt) ± bevacizumab (Bev).

Table IV. Intracranial remission in NS-NSCLC patients with brain metastasis after treatment with pemetrexed-platinum–based chemotherapy (Pem-Pt) ± bevacizumab (Bev). Data are given as percentages of patients.

Parameter	Pem-Pt (n = 27)	Pem-Pt + Bev (n = 15)	*P*
Response			0.0105[a]
CR	0	6.67	
PR	22.22	60.00	
SD	51.85	33.33	
PD	25.93	0	
ORR (CR + PR)	22.22	66.67	0.0045[b]
OR (95% CI)	Ref.	7.000 (1.717–28.545)	0.0067[c]

CR = complete response; OR = odd ratio; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.
[a] Fisher exact test.
[b] χ^2 test.
[c] Univariate logistic regression.

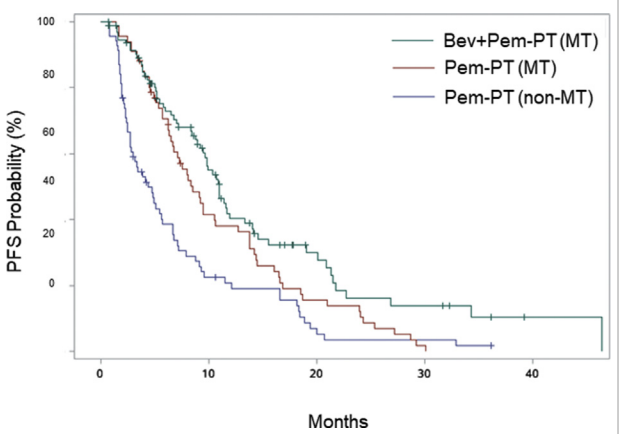

Figure 4. Progression-free survival (PFS) after maintenance therapy (MT) with pemetrexed + bevacizumab in patients with NS-NSCLC.

investigated. There were no observations of AEs of grade ≥ III, or any unexpected AEs, reported in patients. AEs of grade I or II are shown in Table V. One case of grade I epistaxis was reported in 1 patient in the Pem-Pt + Bev group.

DISCUSSION

Currently, standard first-line treatment of advanced NSCLC remains a platinum (cisplatin/carboplatin)-based chemotherapy doublet. Second-line therapeutic agents include gemcitabine, paclitaxel,[9,10] and pemetrexed.[21] Among these, pemetrexed, an antineoplastic inhibitor of folate-dependent metabolic

Table V. Grades I and II[a] adverse events with pemetrexed-platinum–based chemotherapy (Pem-Pt) ± bevacizumab (Bev) in patients with NS-NSCLC. Data are given as number (%) of patients.

Adverse Event	Pem-Pt (n = 140)	Pem-Pt + Bev (n = 96)
Vomiting	42 (30.0)	26 (27.1)
Anemia	33 (23.5)	14 (14.6)
WBC count decreased	22 (15.7)	10 (10.4)
Platelet count decreased	10 (10.4)	7 (7.3)
Hypertension	0	20 (20.8)
Epistaxis	0	10 (10.4)
Proteinuria	0	6 (6.2)

WBC = white blood cell.
[a] None of thepatients experienced adverse events of grade III or IV.

processes and DNA synthesis, greatly prevents cell proliferation and tumor progression.[22] Several studies have demonstrated that patients with NS-NSCLC who received the pemetrexed-cisplatin regimen had greater overall survival when compared with those who received gemcitabine-cisplatin therapy,[19,23,24] and pemetrexed-cisplatin was also associated with a better safety profile.[19,25] Accordingly, the European Society of Medical Oncology guideline recommends pemetrexed over gemcitabine in patients with NS-NSCLC.[26] In addition, the US Food and Drug Administration has approved the Pem-Pt regimen as first-line therapy for locally advanced or metastatic NSCLC,[27] and a single-agent pemetrexed regimen is indicated as second-line therapy.[28]

Antiangiogenesis therapy is a conventional treatment for tumors. Bevicizumab, a VEGF antagonist, can inhibit the binding of VEGF to the receptors of the vascular endothelial cell surface and reduce blood vessel formation in the tumor, thus preventing tumor progression. Also, many proangiogenic growth factors are associated with high vascular permeability, and their withdrawal can reverse the effect. Bevicizumab has been reported to reduce the permeability of blood vessels to macromolecules,[29] therefore reducing the interstitial tissue pressure in the tumor to enhance the delivery of the chemotherapeutic drug and improve chemotherapy efficacy.[30] Based on these findings, bevacizumab is currently the only antiangiogenesis agent approved for the first-line treatment of advanced NSCLC.

Previous studies,* such as PointBreak, AVAiL, SAiL, ARIES, and BEYOND, have demonstrated greater ORR and PFS with bevicizumab-containing chemotherapy over chemotherapy alone in patients with advanced NSCLC.[17,18,31–34] The Pointbreak study was the first to evaluate pemetrexed-carboplatin + bevacizumab and paclitaxel-carboplatin + bevacizumab in patients with advanced NSCLC and demonstrated a significantly improved PFS in both arms.[35] Although ARIES expanded the study of bevacizumab to a broader population in clinical practice,[36] the Asian population was excluded. The BEYOND study from China evaluated the effectiveness of bevacizumab in combination with paclitaxel-platinum in a highly selected patient cohort and showed a clinical benefit of bevacizumab in Chinese patients with advanced NS-NSCLC (PFS, 9.2 months).[16] The SAiL–East Asian subgroup study, which addressed the effectiveness of cisplatin-based chemotherapy plus bevacizumab in NS-NSCLC, showed a greater PFS (8.8 months) in Chinese patients compared with the worldwide population.[37] A similar conclusion was drawn from the AVAiL–East Asian subgroup study of cisplatin-gemcitabine plus bevacizumab in Asian patients with NS-NSCLC (PFS, 8.2 months).[33]

* 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; AVAiL: Efficacy and Safety of Bevacizumab-based Therapy in Elderly Patients with Advanced or Recurrent Nonsquamous Non-small Cell Lung Cancer in the Phase III BO17704 Study; SAiL: Safety and Efficacy of First-line Bevacizumab-based Therapy in Advanced Nonsquamous Non-small-cell Lung Cancer (SAiL, MO19390): A Phase 4 Study; and ARIES: Safety and Effectiveness of Bevacizumab-containing Treatment for Non-small-cell lung Cancer: Final Results of the ARIES Observational Cohort Study.

However, several crucial issues cannot be addressed by these studies. First, most of the chemotherapeutic regimens used in these cohort studies were paclitaxel-platinum, and further exploration of the effectiveness of Pem-Pt + Bev in advanced NS-NSCLC is required. Second, these studies have not included patients with brain metastasis, despite the fact that 25%−30% of patients with NSCLC are diagnosed with brain metastasis in clinical practice,[38] and the brain is also a common recurrence site.[10,11] Therefore, the effectiveness of the a bevacizumab-containing regimen in patients with NS-NSCLC and brain metastasis should be addressed. Third, an optimal regimen, including the choice of maintenance treatment, needs to be established. Fourth, the safety profile of bevacizumab in patients with advanced NS-NSCLC in China with complications needs to be further determined. Fifth, with regard to histology, gene mutation status, and chemotherapy sensitivity, the Chinese population differs from the Western population. Therefore, we conducted a study in clinical practice in a Chinese cohort with NS-NSCLC to evaluate the effectiveness and safety profile of the Pem-Pt + Bev regimen. Our findings from clinical practice include those from assessments of the following characteristics: pleural effusion and brain metastasis.

Our results from a 233-patient cohort further support the clinical benefit of bevacizumab in patients with advanced NS-NSCLC in China. Compared with the Pem-Pt regimen, the Pem-Pt + Bev regimen was associated with a significantly longer median PFS (10.97 vs 6.67 months; $P = 0.0002$) and a substantially higher ORR (63.92% vs 20.74%; odds ratio = 7.63; 95% CI , 3.96−14.67; $P < 0.0001$) in the overall population. Also, brain metastasis has been reported to be a significant cause of death in patients with malignant tumors and is highly prevalent in patients with NS-NSCLC.[38] Consistent with the fact that bevacizumab can inhibit tumor angiogenesis, improve tumor microvascular structure, and increase the permeability of blood vessels to relieve the cerebral edema caused by brain metastasis, our study revealed that the Pem-Pt + Bev regimen could prolong PFS in patients with brain metastasis. Moreover, patients receiving Pem-Pt + Bev gained a sustained intracranial remission from brain metastasis, as demonstrated by a greater ORR. Interestingly, a recent study demonstrated that the regulation of c-Jun N-terminal kinase/P38/phosphoinositide 3-kinase by transforming growth factor β_1 led to down-expression of nonmuscle myosin IIA, which promoted epithelial-to-mesenchymal transition and brain metastasis in lung cancer.[39] These findings lay a foundation for the combined regimen of a transforming growth factor β1 inhibitor and bevacizumab in the treatment of brain metastasis in NSCLC. Furthermore, bevacizumab can reduce tissue interstitial pressure to increase the delivery of chemotherapy drugs to the cancer cells, promote the normalization of tumor blood vessels, and effectively inhibit the formation of pleural effusion. Likewise, our results show that the Pem-Pt + Bev regimen could prolong the PFS in patients with pleural effusion.

Previously, AVAPERL (Randomized Phase III Trial of Maintenance Bevacizumab With or Without Pemetrexed After First-line Induction With Bevacizumab, Cisplatin, and Pemetrexed in Advanced Nonsquamous Non-small-cell Lung Cancer)[40] revealed a survival benefit of bevacizumab-containing pemetrexed maintenance treatment in patients with NS-NSCLC after first-line bevacizumab-containing pemetrexed-cisplatin treatment. Consistently, our study demonstrated that the Pem-Pt + Bev−treated patients choosing maintenance therapy not only showed a longer median PFS than did Pem-Pt−treated patients choosing maintenance therapy but also a longer median PFS than in those whose treatment was interrupted after induction in the Pem-Pt−treated group. Therefore, maintenance therapy may be an essential survival factor in patients in NS-NSCLC. Moreover, only AEs of grade I or II were observed at the dose of 7.5 mg/kg of bevacizumab in this study. Taken together, the findings from our study support that the bevacizumab-containing Pem-Pt regimen is associated with a longer PFS compared with the Pem-Pt regimen in clinical practice in the Chinese population with NS-NSCLC.

Our study may have had several inherent limitations, such as its retrospective nature, small sample size, and the fact that it was conducted at a single institution. All of these factors may have caused biases and affect the power and significance of the findings. In the future, prospective cohort studies should be conducted

to gain better insight into bevacizumab-containing Pem-Pt doublet chemotherapy in patients with advanced NS-NSCLC in China and to strengthen our conclusions.

Taken together, our study provides essential clinical insights into the treatment of patients with advanced NS-NSCLC in China in clinical practice. We demonstrate that the first-line bevacizumab-containing Pem-Pt chemotherapy was well tolerated and may significantly prolong PFS outcomes, including in patients with pleural effusion or brain metastasis. Moreover, bevacizumab-containing pemetrexed maintenance treatment was demonstrated to be a beneficial survival factor.

Conflict of Interest

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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All of the authors assume full responsibility for data collection, analyses, and interpretations. X.Li and M. Abbas performed the study design, data collection, data interpretation and drafted the manuscript. Y.Li, Y. Teng, Y. Fang and S. Yu facilitated data collection. L. Wang and M. Shi were involved in the design of the study and helped in drafting the manuscript. Y. Wen performed the statistical analysis, data interpretation and figure creation. C. Wang helped with the manuscript revision. All authors approved the final manuscript.

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