Comparison of chemotherapy plus bevacizumab vs. chemotherapy alone as third-line treatment or beyond for advanced non-small cell lung cancer: A propensity score-matched analysis

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Abstract. The addition of bevacizumab to chemotherapy has demonstrated efficacy as a first-line treatment for non-small cell lung cancer (NSCLC). Whether this combination is effective as a salvage treatment for patients with NSCLC remains unclear. The present retrospective study was designed to compare the efficacy and safety of chemotherapy plus bevacizumab with chemotherapy alone as a third-line, or continuing, treatment for patients with NSCLC. Between January 2011 and June 2016, a total of 38 patients with stage IV NSCLC who had received chemotherapy plus bevacizumab subsequent to failure of ≥2 prior regimens were matched with 38 patients who had received chemotherapy alone using propensity score matching from a dataset of 165 patients. The variables that were analyzed included age, sex, smoking history, histology, epithelial growth factor receptor mutation status, number of prior regimens and type of chemotherapy regimen. Univariate and multivariate analyses were used to evaluate the prognostic factors for survival outcomes and tumor response, and toxicity analyses were performed. The objective response rate (ORR) and disease control rate (DCR) were improved in patients who underwent chemotherapy-bevacizumab treatment compared with chemotherapy alone (ORR, 23.7 vs. 5.3%, P<0.001; DCR, 65.8 vs. 31.6%, P<0.001). Progression-free survival was prolonged in the chemotherapy-bevacizumab group compared with the chemotherapy-alone group (median, 3.9 vs. 2.2 months; HR, 0.54; 95% CI, 0.32-0.89, P=0.014). Incidence of ≥grade 3 adverse events was low and similar across the groups. The combination of chemotherapy and bevacizumab is a potentially effective and safe alternative salvage treatment for patients with NSCLC who have not received bevacizumab treatment previously.

Introduction

Lung cancer is the leading cause of cancer-associated mortalities in China (1). Non-small cell lung cancer (NSCLC) accounts for 80% of all cases of lung cancer worldwide (2), with the majority of patients presenting with progressive disease. Platinum-based chemotherapy remains the standard first-line treatment for advanced NSCLC (3). The identification of activating driver mutations in the epidermal growth factor receptor (EGFR) has changed the course of therapy for patients with NSCLC harboring these mutations (4,5). As second-line treatment, docetaxel, pemetrexed and erlotinib exhibit low objective response rates (ORR) and short progression-free survival (PFS) (6-8). The use of immune checkpoint inhibitors such as nivolumab and pembrolizumab may prolong overall survival (OS) and duration of response in patients with NSCLC, particularly for those who express programmed death ligand-1 (PD-L1) (9-11).

At present, there are no guidelines for the systemic treatment for patients with NSCLC who have failed 2 therapy regimens. In a previous retrospective study, although a number of patients received third-line treatment, the results of salvage treatment were not satisfactory (12). With additional first- and second-line therapies being made available, the number of patients with NSCLC who are candidates for third-line, or continuing, treatments has increased during the previous decade. Therefore, an effective treatment approach is urgently required, particularly for patients with neither targetable molecular aberrations nor PD-L1 expressions.

Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (13), and has been demonstrated to be effective when used in tandem with a number of chemotherapeutic agents for the treatment of patients with NSCLC (14-16). A combination of carboplatin, paclitaxel and bevacizumab has been approved by the United States of

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America Food and Drug Administration as a first-line treatment for advanced NSCLC due to the results of the Eastern Cooperative Oncology Group (ECOG) 4599 study (14). A combination of cisplatin, gemcitabine and bevacizumab or carboplatin, pemetrexed and bevacizumab has also exhibited encouraging efficacy as a first-line treatment (15,16).

Several studies have also evaluated using bevacizumab as an adjunct to salvage treatments: One phase II study evaluated pemetrexed plus bevacizumab as second-line treatment for patients with NSCLC, and demonstrated a disease control rate (DCR) of 50.0%, a median PFS of 4.0 months and a median OS of 8.6 months (17). An additional retrospective study identified the efficacy of weekly paclitaxel and bevacizumab as a fourth-line, and continuing, treatment for patients with NSCLC (18).

The combination of chemotherapy and bevacizumab as a third-line, or continuing, treatments in NSCLC has not been studied, and its efficacy remains unclear. For patients who have not received bevacizumab previously, the combination of bevacizumab and chemotherapy may be an effective salvage treatment based on encouraging antitumor activity observed as a first-line treatment (14-16). Therefore, the present study was designed to compare the efficacy and safety of chemotherapy plus bevacizumab (chemotherapy-bevacizumab group) with chemotherapy alone (chemotherapy-alone group) as a third-line, or continuing, treatment for patients with NSCLC using propensity score matching (PSM).

Materials and methods

Patients. The present retrospective analysis of 165 patients with stage IV NSCLC, diagnosed according to the 7th edition of American Joint Committee on Cancer staging system (19), who had received single-agent chemotherapy with or without bevacizumab following the failure of ≥2 prior standard systemic regimens was performed at the Department of Thoracic Oncology, West China Hospital (Chengdu, China) between January 2011 and June 2016. Inclusion criteria of patients were: >18 years of age, ECOG performance status of 0-1 (20,21), measurable lesions as defined by Response Evaluated Criteria in Solid Tumors (RECIST; version 1.1) (22), and histological or cytological confirmation of adenocarcinoma, or squamous cell and adenosquamous carcinoma but without a central lesion or lesion abutting major blood vessels, history of hemoptysis or presence of cavitation and concomitant use of full-dose anti-coagulants. Patients who had previously received bevacizumab were not eligible. All patients enrolled underwent computed tomography scanning. Baseline clinical characteristics included age, sex, smoking history, histology, EGFR mutation status, number of prior regimens and type of chemotherapy regimen.

Treatment. All patients had received single-agent chemotherapy with or without bevacizumab. Single-agent chemotherapy included gemcitabine (days 1 and 8, 1,000 mg/m^2), pemetrexed (day 1, 500 mg/m^2), paclitaxel (day 1, 150 mg/m^2) and docetaxel (day 1, 75 mg/m^2). Bevacizumab (Avastin®; Roche Diagnostics GmbH, Mannheim, Germany) was administered intravenously at a dose of 7.5 mg/kg on day 1. Combined and monotherapy were repeated every 3 weeks and continued until disease progression or development of unacceptable toxicity.

Evaluation of efficacy, survival and toxicity. Efficacy evaluation was performed every 6 weeks following the administration of treatment. The treatment response was assessed with RECIST 1.1 as follows: Complete response (CR); partial response (PR); stable disease (SD); and progressive disease (PD). The ORR included CR and PR. The DCR included CR, PR and SD. OS was measured from the first day of chemotherapy-bevacizumab or chemotherapy alone to the day of mortality or last follow-up. PFS was defined as the time between the initiation of treatment and disease progression or mortality from any cause. The adverse events (AEs) of treatment were graded the by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) (23).

Statistical analysis. All statistical analyses were performed using SPSS (version 20.0; IBM Corp., Armonk, NY, USA). To minimize the effects of potential confounding factors between the chemotherapy-bevacizumab and chemotherapy-alone groups, PSM was performed. Associations between the treatment and baseline clinical characteristics were analyzed by Pearson's χ^2 tests. Patients who had received chemotherapy plus bevacizumab were matched 1:1 with patients who had received chemotherapy alone using PSM based on the variables that were significantly different between the two groups. Propensity scores were generated by using a multivariate logistic regression (24). Patients were considered a match if the absolute difference in their propensity scores was ≤0.02.

In the matched dataset, tumor responses and AEs were compared using Pearson's χ^2 and Fisher's exact tests. Survival curves were compared using the Kaplan-Meier method using the log-rank test. Univariate and multivariate Cox proportional hazards regression were used to evaluate the prognostic factors and to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for OS and PFS. Subgroup analyses of OS and PFS were also performed by the Kaplan-Meier method using the log-rank test. All clinical variables were included in the multivariate regressions, regardless of their univariate significance level. Two-sided P<0.05 were considered to indicate a statistically significant difference.

Results

Patient characteristics and treatment. From January 2011 to June 2016, a total of 165 patients who had received chemotherapy plus bevacizumab (n=43) or chemotherapy alone (n=122) as third-line, or continuing treatments were initially enrolled in the present study. For PSM-matched variables, the number of prior regimens (P=0.009) and type of chemotherapy regimen (P<0.001) were significantly different between the two groups. A total of 38 patients in the chemotherapy-bevacizumab group were then matched to 38 patients in the chemotherapy-alone group. The cut-off day of the present study was December 2016, and the median follow-up of all patients was 7.9 months (range, 1.1-62.9 months).

The baseline clinical characteristics for patients pre- and post-PSM are summarized in Table I. The median age of patients was 52 years (range, 40-71 years) in the chemotherapy-bevacizumab group and 49 years (range, 38-76 years) in the chemotherapy-alone group. In the chemotherapy-bevacizumab group, 34 (34/38; 89.5%) comprised

Table I. Baseline clinical characteristics for patients in the chemotherapy-bevacizumab group vs. chemotherapy alone group prior and subsequent to propensity score matching.

A, Unmatched dataset

Characteristics	Chemotherapy-bevacizumab (n=43)	Chemotherapy alone (n=122)	P-value
Age, years			0.844
Median (range)	52 (37-72)	56 (27-76)	
≤60	32	88	
>60	11	34	
Sex, n			0.287
Male	19	67	
Female	24	55	
Smoking history, n			0.583
Current/previous	14	47	
Never	29	75	
Histology, n			0.800
Adenocarcinoma	38	105	
Squamous cell/ adenosquamous carcinoma	5	17	
EGFR mutation status			0.716
Mutant type[a]	17	44	
Wild-type/unknown	26	78	
Number of prior regimens[b], n			0.009
Median (range)	3 (2-5)	2 (2-5)	
≤3	28	103	
>3	15	19	
Chemotherapy regimen, n			<0.0001
Gemcitabine	30	39	
Pemetrexed	5	31	
Paclitaxel	3	8	
Docetaxel	5	44	

B, Matched (1:1) dataset

Characteristics	Chemotherapy-bevacizumab (n=38)	Chemotherapy alone (n=38)	P-value
Age, years			1.000
Median (range)	52 (40-71)	49 (38-76)	
≤60	30	31	
>60	8		
Sex			0.492
Male	17	21	
Female	21	17	
Smoking history, n			0.240
Current/previous	26	20	
Never	12	18	
Histology, n			1.000
Adenocarcinoma	34	35	
Squamous cell/ adenosquamous carcinoma	4	3	
EGFR mutation status			0.641
Mutant type[a]	17	14	
Wild-type/unknown	21	24	

Table I. Continued.

Characteristics	Chemotherapy-bevacizumab (n=38)	Chemotherapy alone (n=38)	P-value
Number of prior regimens[b], n			1.000
Median (range)	3 (2-5)	3 (2-4)	
≤3	28	28	
>3	10	10	
Chemotherapy regimen, n			1.000
Gemcitabine	25	25	
Pemetrexed	5	5	
Paclitaxel	3	3	
Docetaxel	5	5	

EGFR, epidermal growth factor receptor. [a]Mutant type included the exon 19 deletion and exon 21 L858R mutations. [b]Prior regimens included chemotherapy, EGFR tyrosine kinase inhibitors and anaplastic lymphoma kinase inhibitors.
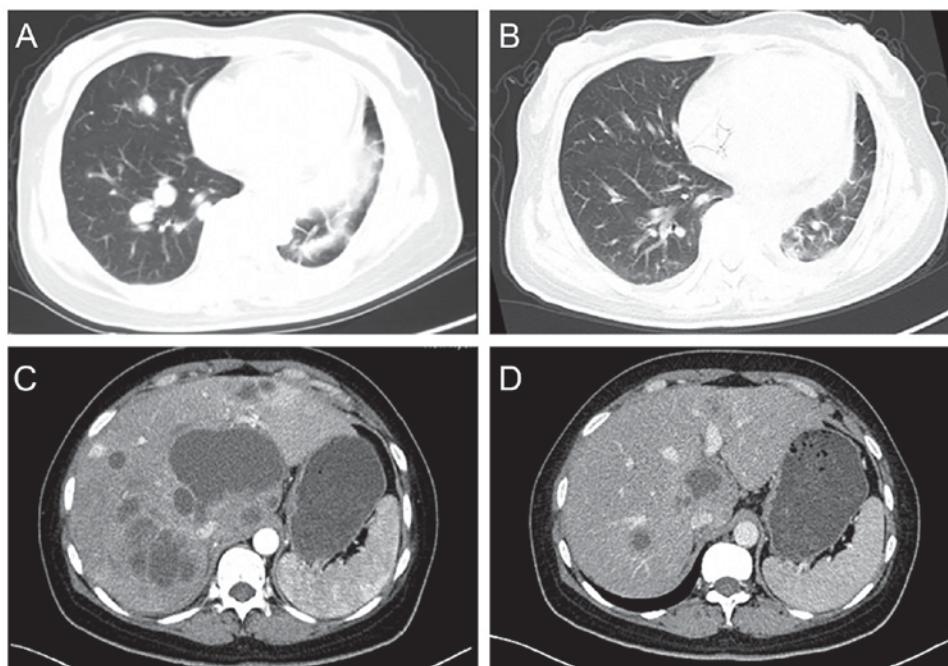

Figure 1. Examples of response to treatment with chemotherapy plus bevacizumab. CT images of a 51-year-old female with stage IV adenocarcinoma following (A) pre-treatment with chemotherapy-bevacizumab on 1st December, 2012 and (B) post-treatment with chemotherapy-bevacizumab on 6th February, 2013. CT images of a 42-year-old female with stage IV squamous cell carcinoma following (C) pre-treatment with chemotherapy plus bevacizumab on 9th May, 2015 and (D) post-treatment with chemotherapy-bevacizumab on 10th July, 2015. Images A and C were captured at baseline. Images B and D were captured following 2 cycles of chemotherapy-bevacizumab.

patients with adenocarcinoma, 2 (2/38; 5.3%) with squamous cell carcinoma and 2 (2/38; 5.3%) with adenosquamous carcinoma. In the chemotherapy-alone group, 35 (35/38; 92.1%) comprised patients with adenocarcinoma, 2 (2/38; 5.3%) with squamous cell carcinoma and 1 (1/38; 2.6%) with adenosquamous carcinoma. The median number of prior regimens was 3 (range, 2-5) in the chemotherapy-bevacizumab group and 3 (range, 2-4) in the chemotherapy-alone group. A total of 10 (10/38; 26.3%) patients had failed >3 prior regimens in the two groups.

The majority (25/38; 65.8%) of patients received gemcitabine as their monotherapy or combined therapy with bevacizumab. All patients received ≥1 cycle of treatment. The median number of cycles of treatment was 3 (range, 1-10) in the chemotherapy-bevacizumab group and 2 (range, 1-6) in the chemotherapy-alone group.

Tumor response. In the chemotherapy-bevacizumab group, 9 patients achieved a PR, of which 3 were squamous cell or adenosquamous carcinoma, and 16 exhibited SD, of which 1 was adenosquamous carcinoma. In the chemotherapy-alone group, 2 patients achieved a PR and 10 exhibited SD. There was a significant improvement in ORR and DCR for the chemotherapy-bevacizumab group compared with the chemotherapy-alone group (ORR, 23.7 vs. 5.3%, respectively, $P<0.001$; DCR, 65.8 vs. 31.6%, respectively, $P<0.001$).
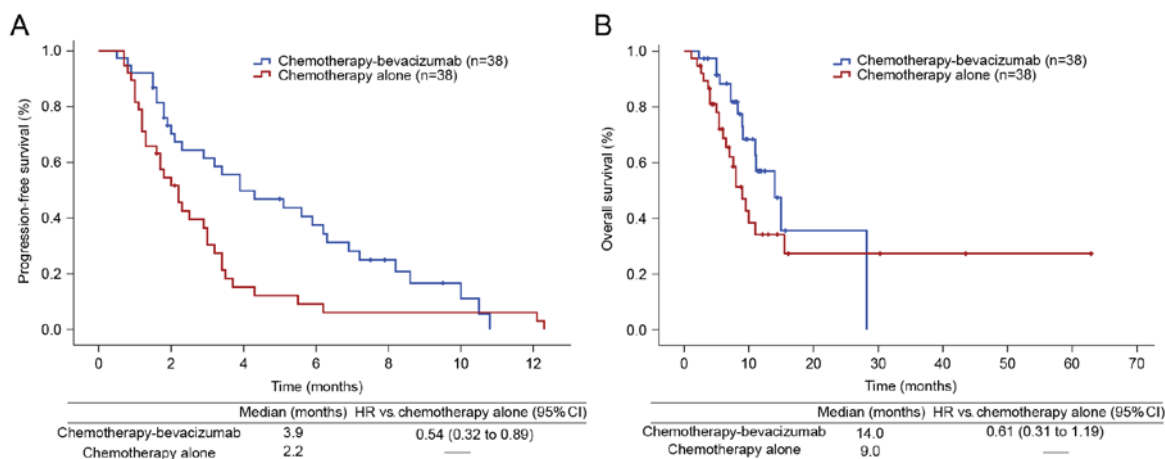
Figure 2. Kaplan-Meier survival curves from the matched dataset using (A) progression-free survival and (B) overall survival. HR, hazard ratio; CI, confidence interval.

Computed tomography scans of 2 patients with PR are shown in Fig. 1. Of these patients, 1 patient was a 51-year-old female with stage IV adenocarcinoma, who received gemcitabine plus bevacizumab as a fourth-line therapy. This patient received a total of 6 cycles of treatment, and following 2 cycles of treatment, there was a marked reduction in size of the pulmonary lesions. The PFS of the patient was 3.9 months, but she succumbed subsequent to follow-up for 9.1 months. The other patient was a 42-year-old female with stage IV squamous cell carcinoma, who received gemcitabine plus bevacizumab as a fifth-line therapy, and primarily targeted lesions in the liver. The hepatic lesions were notably reduced in size following 2 cycles of treatment. This patient exhibited a total of 10 months for PFS and survived until the cut-off point.

Survival outcome. In the univariate analysis, bevacizumab treatment was the only significant prognostic factor for PFS, but not for OS (data not shown). The duration of PFS was longer for the chemotherapy-bevacizumab group compared with the chemotherapy-alone group (median, 3.9 vs. 2.2 months, respectively; HR, 0.54; 95% CI, 0.32-0.89; P=0.014; Fig. 2A). The duration of OS non-significantly increased with chemotherapy-bevacizumab treatment compared with chemotherapy alone (median, 14.0 vs. 9.0, respectively; HR, 0.61; 95% CI, 0.31-1.19; P=0.141; Fig 2B). Smoking was associated with poor OS (HR, 2.00; 95% CI, 1.04-3.86; P=0.033). Multivariate analysis also demonstrated that bevacizumab treatment was the only independent prognostic factor for PFS (HR, 0.48; 95% CI, 0.27-0.85; P=0.011; Table II), and age was the only independent risk factor for OS (HR, 4.19; 95% CI, 1.17-14.97; P=0.027; Table II).

In the subgroup analyses, PFS was significantly prolonged following chemotherapy-bevacizumab treatment compared with chemotherapy alone in the following subgroups: Male sex; current or former smokers; adenocarcinoma subtypes; EGFR wild-type or unknown; and patients with ≤3 prior regimens (Table III). PFS was notably prolonged in the subgroup of patients treated with gemcitabine (Table III). OS was significantly prolonged for chemotherapy-bevacizumab treatment compared with chemotherapy alone in the subgroup of patients with >3 prior regimens (Table III).

Toxicity. Hematological and non-hematological toxicities of patients in the two groups are summarized in Table IV. The incidence of severe (≥ grade 3) AEs was low and comparable in the two groups (chemotherapy-bevacizumab vs. chemotherapy alone, 28.9 vs. 26.3%). In the chemotherapy-bevacizumab group, the most common AEs of all grades were leukopenia (19/38; 50.0%), increased alanine transaminase (ALT) or aspartate transaminase (AST; 17/38; 44.8%) and fatigue (16/38; 42.1%). In the chemotherapy-alone group, the most common AEs of all grades were nausea (16/38; 42.1%), leukopenia (15/38; 39.4%) and increased ALT or AST (14/38; 36.8%). The rates of bleeding (P=0.001) and hypertension (P=0.025) were significantly increased in the chemotherapy-bevacizumab group compared with the chemotherapy-alone group. Although 15 (15/38; 39.5%) patients in the chemotherapy-bevacizumab group experienced grade 1/2 bleeding, of which 3 were squamous cell carcinoma, there were no reports of ≥grade 3 bleeding events.

Continuous bevacizumab treatment following disease progression. In the chemotherapy-bevacizumab group, 22 patients received post-progression treatment, of which 14 continued to receive bevacizumab. This treatment regimen included docetaxel plus bevacizumab in 4 patients (4/14; 28.6%), pemetrexed plus bevacizumab in 4 patients (4/14; 28.6%), paclitaxel plus bevacizumab in 3 patients (3/14; 21.4%), gemcitabine plus bevacizumab in 2 patients (2/14; 14.3%) and vinorelbine plus bevacizumab in 1 patient (1/14; 7.1%). The median number of cycles of treatment was 2 (range, 1-4). Among the 14 patients, one patient had not received an initial evaluation of efficacy as they had not completed two cycles of treatment. Of the remaining 13 patients whose response was assessed, PR was observed in 2 patients (2/13; 15.4%) and SD was observed in 6 patients (6/13; 46.1%). PFS was 3.4 months (95% CI, 2.8-4.0 months). No incident ≥grade 3 AEs were observed.

Discussion

There is currently no standard systemic therapy for third-line, or continuing, treatments of NSCLC. With an increasing number of patients who meet the criteria for receiving third-line treatment or beyond, it is imperative to optimize therapy regimens

Table II. Multivariate Cox regression analyses for progression-free survival and overall survival in patients from the matched dataset.

A, Progression-free survival

Variables	HR (95% CI)	P-value
Groups		
Chemotherapy-bevacizumab vs. chemotherapy alone	0.48 (0.27-0.85)	0.011
Age, years		
≤60 vs. >60	0.95 (0.49-1.88)	0.892
Sex		
Female vs. male	0.82 (0.34-1.97)	0.656
Smoking history		
Current/previous vs. never	1.15 (0.48-2.77)	0.753
Histology		
Adenocarcinoma vs. squamous cell/adenosquamous carcinoma	1.25 (0.47-3.36)	0.655
EGFR mutation status		
Wild-type/unknown vs. mutant type	0.74 (0.41-1.36)	0.333
Number of prior regimens		
≤3 vs. >3	1.06 (0.57-1.98)	0.858
Chemotherapy regimen		0.326
Gemcitabine	Ref.	
Pemetrexed	0.50 (0.21-1.24)	0.137
Paclitaxel	1.42 (0.54-3.77)	0.481
Docetaxel	1.31 (0.58-2.97)	0.511

B, Overall survival

Variables	HR (95% CI)	P-value
Group		
Chemotherapy-bevacizumab vs. chemotherapy alone	0.53 (0.26-1.07)	0.076
Age, years		
≤60 vs. >60	4.19 (1.17-14.97)	0.027
Sex		
Female vs. male	1.30 (0.36-4.74)	0.694
Smoking history		
Current/previous vs. never	3.32 (0.86-12.76)	0.081
Histology		
Adenocarcinoma vs. squamous cell/adenosquamous carcinoma	1.33 (0.29-6.11)	0.711
EGFR mutation status		
Wild-type/unknown vs. mutant type	1.10 (0.51-2.37)	0.812
Number of prior regimens		
≤3 vs. >3	1.05 (0.49-2.26)	0.908
Chemotherapy regimen		0.064
Gemcitabine	Ref.	
Pemetrexed	0.19 (0.05-0.84)	0.029
Paclitaxel	0.25 (0.05-1.24)	0.090
Docetaxel	0.57 (0.21-1.57)	0.275

EGFR, epidermal growth factor receptor; HR, hazard ratio; CI, confidence interval; Ref, reference.

Table III. Subgroup analyses in patients with chemotherapy-bevacizumab vs. chemotherapy alone from the matched dataset.

Subgroups	Median PFS (months)	Median OS (months)	HR (95% CI)	P-value
Male sex	5.6 vs. 2.0	-	0.24 (0.10-0.54)	<0.0001
Current/former smokers	4.3 vs. 2.2	-	0.32 (0.13-0.78)	0.008
Adenocarcinoma	3.9 vs. 2.2	-	0.59 (0.35-0.99)	0.037
EGFR wild-type/unknown	6.3 vs. 2.9	-	0.26 (0.12-0.58)	<0.0001
Prior regimens ≤3	3.9 vs. 2.2	-	0.55 (0.30-0.99)	0.038
Gemcitabine	4.3 vs. 2.5	-	0.55 (0.30-1.01)	
Prior regimens >3	-	14.0 vs. 5.4	0.29 (0.09-0.92)	0.025
Docetaxel	-	14.0 vs. 8.0	0.01 (0.00-37.70)	

EGFR, epidermal growth factor receptor; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Table IV. Toxicity grades of patients in the two groups from the matched dataset.

	No. of patients (%)			
	Chemotherapy-bevacizumab (n=38)		Chemotherapy alone (n=38)	
Toxicity	Grade 1/2	Grade ≥3	Grade 1/2	Grade ≥3
Hematological toxicity				
Leukopenia	14 (36.8)	5 (13.2)	11 (28.9)	4 (10.5)
Neutropenia	11 (28.9)	3 (7.9)	9 (23.7)	4 (10.5)
Anemia	15 (39.5)	0 (0.0)	12 (31.6)	1 (2.6)
Thrombocytopenia	6 (15.8)	1 (2.6)	7 (18.4)	2 (5.3)
Non-hematological toxicity				
Increased ALT or AST	15 (39.5)	2 (5.3)	13 (34.2)	1 (2.6)
Fatigue	14 (36.8)	2 (5.3)	12 (31.6)	0 (0.0)
Nausea	12 (31.6)	0 (0.0)	15 (39.5)	1 (2.6)
Vomiting	7 (18.4)	0 (0.0)	7 (18.4)	1 (2.6)
Rash	4 (10.5)	0 (0.0)	3 (7.9)	0 (0.0)
Joint or muscle pain	4 (10.5)	0 (0.0)	1 (2.6)	0 (0.0)
Hypertension	6 (15.8)	0 (0.0)	0 (0.0)	0 (0.0)
Bleeding	15 (39.5)	0 (0.0)	2 (5.3)	0 (0.0)
Proteinuria	4 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)

ALT, alanine transaminase; AST, aspartate transaminase.

for eligible candidates. When combined with chemotherapy, bevacizumab has demonstrated efficacy as a first-line treatment for NSCLC (14-16), and it may also be effective as a salvage treatment for bevacizumab treatment-naïve patients with NSCLC. The present retrospective study aimed to additionally evaluate the efficacy and safety of bevacizumab in combination with chemotherapy as a third-line, or continuing, treatment for NSCLC patients. The results of the present study indicated favorable clinical outcomes with chemotherapy-bevacizumab therapy.

The values for ORR (23.7%) and DCR (65.8%) for the chemotherapy-bevacizumab treatment observed in the present study were higher compared with the values obtained previously, where 6.45% was reported for ORR and 54.84% was reported for DCR by Ding *et al* (25). Improvements in ORR and DCR in NSCLC were also noted with the chemotherapy-bevacizumab

treatment in other studies (17,26). Previously, ULTIMATE, a randomized, phase III study evaluated the efficacy and safety of bevacizumab as a salvage treatment for patients with NSCLC, who had previously failed first-, second- and third-line treatments and were randomized to receive weekly paclitaxel and bevacizumab or docetaxel alone. It was reported that significant improvement was observed in ORR for bevacizumab compared with docetaxel alone (22.5 vs. 5.5%, respectively). Additionally, PFS was prolonged compared with docetaxel alone (5.4 vs. 3.9 months, respectively), but not OS (27). Similarly, in the present study, chemotherapy-bevacizumab prolonged PFS compared with chemotherapy alone (median, 3.9 vs. 2.2 months). However, improvements in PFS did not translate into significant OS benefits. This may be attributed to the enrollment of patients who had failed several regimens

prior to receiving bevacizumab, which may have affected the OS. An additional possibility may be the small sample size in the present study, which may have reduced statistical significance between groups.

In the subgroup analyses, PFS was notably prolonged following chemotherapy-bevacizumab treatment compared with chemotherapy alone in the subgroup of patients treated with gemcitabine (median, 4.3 vs. 2.5 months; HR, 0.55; 95% CI, 0.30-1.01). Gemcitabine may be a prognostic factor for PFS when the sample size of a study is enlarged. Additionally, gemcitabine is rarely employed as a first- or second-line treatment for patients with advanced non-squamous NSCLC (28), so it may be considered an alternative choice for salvage treatment in patients eligible to receive third-line, or continuing, treatments. The majority of patients (25/38; 65.8%) in the present study received gemcitabine as monotherapy or combined therapy with bevacizumab, potentially informing whether gemcitabine-bevacizumab is an effective third-line, or continuing, treatment for patients with NSCLC.

The toxicity of chemotherapy-bevacizumab in the present study was well tolerated. The incidence of severe (≥ grade 3) AEs was low and comparable in the two groups. For AEs of all grades, hematological toxicities were commonly observed in the chemotherapy-bevacizumab group, which was also observed previously with bevacizumab (14-16,26). The high incidence of increased ALT or AST observed in the chemotherapy-bevacizumab group may be due to a high proportion of patients treated with gemcitabine. No severe bleeding events occurred, indicating that hemorrhage was managed.

Patients with squamous NSCLC have generally been excluded from studies investigating bevacizumab treatment, as squamous histology was identified as a possible risk factor for severe (grade ≥3) pulmonary hemorrhage in a phase II study (29). However, patients with squamous histology have been enrolled in a randomized phase IIIb trial, ATLAS (30). A phase II study, BRIDGE, evaluated the safety of carboplatin, paclitaxel and bevacizumab as a first-line treatment for patients with advanced squamous NSCLC and identified that 1 patient (1/31; 3.23%) experienced grade ≥3 pulmonary hemorrhage, but no other AEs. The authors of the BRIDGE study suggested that treatment of squamous NSCLC with bevacizumab should be considered experimental (31). Based on these data, patients with squamous histology were cautiously enrolled in the present study. A total of 4 patients with squamous cell or adenosquamous histology, who received bevacizumab, did not experience grade ≥3 pulmonary hemorrhage. Additionally, all of these patients responded to treatment, where 3 patients exhibited PR and 1 exhibited SD. Although the sample size was small in the present study, efficacy of bevacizumab was demonstrated in patients with squamous NSCLC.

Assessment of the efficacy and safety of patients who were treated with bevacizumab following previous failure of the drug in the present study demonstrated that the majority of patients continued to benefit from the therapy, with an ORR of 14.3%, DCR of 56.2% and PFS of 3.4 months. In patients treated with chemotherapy-bevacizumab, progressive disease may be considered a failure of chemotherapy, but not necessarily of bevacizumab. Patients whose colorectal cancer had progressed with first-line treatment with bevacizumab, but who continued to receive chemotherapy-bevacizumab

treatment beyond first PD, exhibited a statistically significant improvement in survival (32). In a phase II trial which compared docetaxel and docetaxel plus bevacizumab in patients with NSCLC whose disease had progressed following first-line treatment with bevacizumab plus a platinum-based doublet, significant increases in the median PFS was observed, and a longer median OS was reported in the docetaxel plus bevacizumab group (33). To validate these data, the AvaALL trial (ClinicalTrials.gov identifier, NCT01351415) evaluated the efficacy of standard of care (SOC) with or without continuous bevacizumab treatment beyond progression in patients with NSCLC progression following first-line chemotherapy-bevacizumab treatment. Results reported in 2017 ASCO demonstrated that though there was not a significantly longer OS observed in SOC+ bevacizumab compared with SOC (median, 11.86 vs. 10.22 months, P=0.1044), there were significant increases in the PFS was observed in the SOC +bevacizumab groups when patients were administered third-line SOC (median, 4.0 vs. 2.6 months, P=0.045) (34).

There are several limitations in the present study. Firstly, the review was retrospective and monocentric, and the number of patients included was small. Secondly, prior regimens received by patients prior to the administration of bevacizumab in the two groups were different, which may have affected the efficacy.

In conclusion, to the best of our knowledge, this is the first retrospective study to compare the outcomes of chemotherapy-bevacizumab vs. chemotherapy alone as third-line or continuing, treatment for patients with NSCLC who were bevacizumab-treatment naïve. Treatment with chemotherapy-bevacizumab was able to improve DCR and ORR, and prolong PFS in patients with NSCLC. As the number of studies on the efficacy of chemotherapy-bevacizumab as salvage treatment is limited at present, results from the present study may provide guidance for designing treatment regimens for patients with NSCLC. However, the efficacy of chemotherapy-bevacizumab in patients with NSCLC requires additional investigation in prospective trials.

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