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Drug-eluting bead bronchial arterial chemoembolization *vs.* chemotherapy in treating advanced non-small cell lung cancer: comparison of treatment efficacy, safety and quality of life

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Abstract. – OBJECTIVE: This present study aimed to compare the treatment response, survival profile, quality of life (QoL), and safety between drug-eluting bead bronchial arterial chemoembolization (DEB-BACE) and chemotherapy in the treatment of advanced non-small-cell lung cancer (NSCLC).

PATIENTS AND METHODS: Totally, 44 advanced NSCLC patients were analyzed retrospectively and were divided into DEB-BACE group (n=23) and chemotherapy group (n=21). Treatment response, European Organization for Research and Treatment of Cancer QoL Questionnaire–Core 30 (EORTC QLQ-C30), progression-free survival (PFS), overall survival (OS), and adverse events were assessed during the follow-up.

RESULTS: At month (M) 2, M4 and M6 post initial treatment, objective response rate (ORR) was elevated (all p <0.05), and disease control rate (DCR) tended to be higher (without statistical significance) in DEB-BACE group compared with chemotherapy group. Regarding the QLQ-C30 item scores, the scores of physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning were increased, while the scores of nausea and vomiting, dyspnea, constipation were decreased in DEB-BACE group compared with chemotherapy group (all p <0.05). Based on survival profile, DEB-BACE group achieved better PFS and OS compared with chemotherapy group independent of TNM stage, which was also supported by further subgroup analysis and Cox's proportional hazard regression analysis (all p <0.05). Furthermore, two groups all exhibited mild and tolerable adverse events.

CONCLUSIONS: DEB-BACE has the potential to be an additional treatment option with favorable therapeutic efficacy, improved QoL, and tolerable safety for advanced NSCLC patients.

Key Words:
Drug-eluting bead bronchial arterial chemoembolization, Advanced non-small cell lung cancer, Chemotherapy, Therapeutic efficacy, Quality of life.

Introduction

Lung cancer is one of the most common cancers responsible for almost one-quarter of all cancer-related death, according to the global epidemiological data[1,2]. Non-small cell lung cancer (NSCLC), the main histological type of lung cancer, accounts for approximately 85% of all newly diagnosed lung cancer cases[2]. Due to low public awareness about the clinical presentation of NSCLC, about 70% of NSCLC patients are diagnosed at an advanced stage and suffer from poor 5-year survival ranging from 10% to 20%[3,4]. Currently, the primary therapy for advanced NSCLC patients is platinum-based chemotherapy,

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providing a survival benefit to some extent; however, the majority of patients still experience unfavorable prognosis due to relapsed cancer, refractory to chemotherapy, hematologic and neuropsychiatric toxicity[5,6]. Therefore, effective and less toxic therapy is essential for patients with advanced NSCLC to promote their long-term prognosis.

Bronchial artery chemoembolization (BACE) is a technique of drug delivery and embolization performed via injecting anti-tumor drugs with drug carriers and implanting the embolization agents into the tumor feeding artery, promoting the clinical outcomes of patients and providing a palliative treatment option for patients with advanced NSCLC[7-9]. One prior study discloses that advanced NSCLC patients who receive conventional BACE present disease control rate (DCR) of 40.6% and median progression-free survival (PFS) time of 8.2 months, and the main treatment-related adverse events are mild and tolerable nausea, vomiting, anorexia discomfort and mild bone marrow suppression[8]. Compared with conventional BACE, drug-eluting bead (DEB)-BACE utilizes microspheres to load drugs, which more precisely and sustainably releases drugs, and further leads to improved localization of the drugs as well as less systemic toxicity[10-13]. Only one previous study indicates that DEB- BACE is a feasible and tolerable treatment for NSCLC patients[7]. To our knowledge, there was no related study that compared the therapeutic efficacy between DEB-BACE and standard chemotherapy for the treatment of advanced NSCLC. Therefore, in the present study, we retrospectively analyzed the medical records of 44 advanced NSCLC patients and compared the treatment response, quality of life (QoL), survival profile and safety between DEB-BACE and chemotherapy in treating advanced NSCLC patients.

Patients and Methods

Patients

A total of 44 advanced NSCLC patients treated in our hospital from January 2017 to December 2018 were analyzed in this retrospective cohort study. All patients met the following criteria: (1) histopathologically diagnosed as NSCLC; (2) TNM stage IIIB-IV; (3) age within 18-75 years; (4) had one or more measurable lesion according to modified Response Evaluation Criteria in Solid Tumors (RECIST1.1); (5) Eastern Cooperative Oncology Group (ECOG) score no more than 2; (6) treated by DEB-BACE or conventional chemotherapy; (7) without extensive, uncontrolled extrapulmonary metastases; (8) not complicated with other malignancies; (9) clinical data and survival data were complete and available. This study was supported by the Chinese National Natural Science Foundation project (No. 81901935) and the Military Youth Development Program (No. 17QNP034). Informed consent was obtained from all patients or their families.

Data Extraction

Clinical characteristics of patients were extracted from the database of our hospital, which included age, gender, history of smoke, ECOG score, histological type, and TNM stage. Besides, patients' treatment procedures, response assessment, European Organization for Research and Treatment of Cancer quality of life (QoL) Questionnaire–Core 30 (EORTC QLQ-C30) assessment, adverse events, as well as survival data were collected from medical records and follow-up records.

Treatment Procedures

Patients were categorized into DEB-BACE group (N=23) or chemotherapy group (N=21) depending on the treatment they received.

For patients in the DEB-BACE group, the microcatheter was super selectively inserted into the branch of the tumor feeding bronchial artery, then chemotherapy drugs were infused into the branch. The chemotherapy regimens included the pemetrexed (375 mg/m^2) plus carboplatin (225 mg/m^2) for adenocarcinoma (ADC) and the gemcitabine (750 mg/m^2) plus carboplatin (225 mg/m^2) for squamous cell carcinoma (SCC). After infusion chemotherapy, a bottle of Callispheres® (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu Province, China) beads (ranging 300-500 microns in diameter) was used to load epirubicin (1.5 mg/kg) for 30 min, then non-ionic contrast media was added to the beads in a 1:1 ratio, letting stand for 5 min. Subsequently, epirubicin loaded Callispheres® beads were infused into blood-supply bronchial arterial of tumor at a speed of 1 ml/min for chemoembolization. The chemoembolization was suspended when the blood flow in the tumor supply artery was slow and nearly stopped. Five min later, angiography was performed again to determine whether partial supplementary embolization should be administered. If a bottle of Callispheres® beads

was not enough for complete embolization, the blank Callispheres® beads were added to achieve the complete embolization (the blood flow in the tumor supply artery was stopped), which was conducted according to the actual situation of the patient. With regard to subsequent therapy, the repeated DEB-BACE (no more than 3 cycles) was performed for patients with poor response or partial response after first cycle therapy, with a treatment interval of 1 month. As for patients with complete response (CR) and partial response (PR) after first cycle of DEB-BACE therapy, they were treated with pemetrexed (500 mg/m^2) plus carboplatin (300 mg/m^2) by intravenous injection, which was repeated every 21 days (for ADC) or treated with gemcitabine (1000 mg/m^2) plus carboplatin (300 mg/m^2) by intravenous injection repeated every 21 days (for SCC), until intolerance. Additionally, one week before pemetrexed administration, patients were given intramuscular injection of 1000 μg vitamin B12 and 350-1000 μg folic acid (once a day); and patients orally took 4 mg dexamethasone (twice a day) on the day before chemotherapy, day of chemotherapy, and day after chemotherapy.

As for patients in the chemotherapy group, they were treated with pemetrexed (500 mg/m^2) plus carboplatin (300 mg/m^2) by intravenous injection, which was repeated every 21 days for ADC, or treated with gemcitabine (1000 mg/m^2) plus carboplatin (300 mg/m^2) by intravenous injection, which was repeated every 21 days for SCC, until intolerance. Additionally, one week before pemetrexed administration, patients were given intramuscular injection of 1000 μg vitamin B12 and 350-1000 μg folic acid (once a day); and patients orally took 4 mg dexamethasone (twice a day) on the day before chemotherapy, day of chemotherapy and day after chemotherapy.

Treatment Response and QoL Assessment

Treatment response assessment was conducted at 2 months (M2), 4 months (M4) or 6 months (M6) after initial treatment according to the RECIST1.1. The response was categorized as (1) CR: disappearance of any intratumoral arterial enhancement in all target lesions; (2) PR: at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions; (3) stable disease (SD): any cases that did not qualify to be either PR or progressive disease (PD); 4) PD: an increase of at least 20% in the sum of the diameters of the viable (enhancing) target lesions. In addition, objective response rate (ORR) was defined as CR+PR, and DCR was defined as CR+PR+SD. The QoL of patients was evaluated before initial treatment and at M2 using EORTC QLQ-C30 (Version 3). The EORTC QLQ-C30 Version 3 consisted of 30 items covering 15 domains: five function domains (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), 3 symptom domains (fatigue, nausea and vomiting, pain), 1 global health status/QoL domain, and 6 single-item domains (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). The first 28 items of the questionnaire used a 4-point Likert-type response scale ranging from 1 (not at all) to 4 (very much). Items 29 and 30, which assess global health status/QoL, used a response scale ranging from 1 (very poor) to 7 (excellent). All raw data were transformed to a 0-to-100-point scale. Higher scores in functional scales and global health status/QoL scales indicate better functioning and overall QoL, whereas a higher score for the symptom scale/single-item scale represented a worse level of symptom distress[14].

Follow-Up and Survival Assessment

All patients were followed up monthly after initiation of treatment until December 2019. The follow-up examinations included physical examination, medication history, disease progression status, blood routine, liver and kidney function, chest imaging or chest ultrasound, and so on. The PFS and overall survival (OS) were assessed according to the follow-up records. The PFS was defined as the time interval from initiation of therapy to disease progression or patients' death. The overall survival (OS) was defined as the time interval from initiation of therapy to patients' death. No patients lost follow-up during the study period.

Statistical Analysis

SPSS 22.0 statistical software (IBM, Armonk, NY, USA) was used for statistical analysis, and GraphPad Prism 7.02 (GraphPad Software Inc., San Diego, CA, USA) was used for figure plotting. Data were described as mean ± standard deviation (SD), or count (percentage). Comparison between the two groups was determined by Student's *t*-test or Chi-square test. PFS and OS were displayed by Kaplan-Meier curves. Comparison of PFS and OS between groups was determined

by the log-rank test. Factors affecting treatment response were analyzed by univariate and multivariate logistic regression model, and the factors affecting PFS or OS were analyzed by univariable and multivariable Cox's proportional hazard regression model. p-value <0.05 was considered statistically significant.

Results

Comparison of Clinical Characteristics

The mean age of patients in DEB-BACE group and chemotherapy group were 60.5±10.7 years and 59.0±11.5 years, respectively (Table I). There were 12 (52.2%) males and 11 (47.8%) females in DEB-BACE group, meanwhile there were 9 (42.9%) males and 12 (57.1%) females in chemotherapy group. In terms of ECOG score, the number of patients with ECOG score 0, 1 and 2 were 4 (17.4%), 11 (47.8%) and 8 (34.8%) in DEB-BACE group, while 4 (19.0%), 10 (47.6%) and 7 (33.3%) in chemotherapy group, respectively. Regarding the histological type, there were 13 (56.5%) patients with ADC and 10 (43.5%) patients with SCC in DEB-BACE group; whereas there were 12 (57.1%) patients with ADC and 9 (42.9%) patients with SCC in chemotherapy group. Besides, there were 11 (47.8%) patients at TNM stage IIIB and 12 (52.2%) patients at TNM stage IV in DEB-BACE group; while there were 10 (47.6%) patients at TNM stage IIIB and 11 (52.4%) patients at TNM stage IV in chemotherapy group. Importantly, no difference in clinical characteristics was found between the two groups (all p >0.05). More detailed information on clinical characteristics in advanced NSCLC patients was shown in Table I.

Comparison of Treatment Response

At M2 (Figure 1A), M4 (Figure 1B), M6 (Figure 1C) post initial treatment, ORR was higher in DEB-BACE group compared with chemotherapy group (47.8% *vs.* 19.0%, p =0.044 at M2; 56.5% *vs.* 23.8%, p =0.027 at M4; 52.2% *vs.* 19.0%, p =0.023 at M6); furthermore, DCR tended to be higher in DEB-BACE group compared with chemotherapy group while without statistical significance (100.0% *vs.* 85.7%, p =0.060 at M2; 91.3% *vs.* 76.2%, p =0.171 at M4; 87.0% *vs.* 61.9%, p =0.055 at M6).

Comparison of QoL

Before treatment, no difference of QLQ-C30 item scores between DEB-BACE group and chemotherapy group was shown (all p >0.05) (Table II). After treatment, the scores of physical functioning (p =0.011), role functioning (p =0.001), emotional functioning (p =0.004), cognitive functioning (p <0.001), social functioning (p =0.006) were increased in DEB-BACE

Table I. Characteristics of patients.

Parameters	DEB-BACE (N = 23)	Chemotherapy (N = 21)	*p*-value
Age (years), M ± SD	60.5 ± 10.7	59.0 ± 11.5	0.672
> 60 years, No. (%)	13 (56.5)	10 (47.6)	0.555
≤ 60 years, No. (%)	10 (43.5)	11 (52.4)	
Gender, No. (%)			0.537
Male	12 (52.2)	9 (42.9)	
Female	11 (47.8)	12 (57.1)	
History of smoke, No. (%)			0.378
Yes	14 (60.9)	10 (47.6)	
No	9 (39.1)	11 (52.4)	
ECOG score, No. (%)			0.988
0	4 (17.4)	4 (19.0)	
1	11 (47.8)	10 (47.6)	
2	8 (34.8)	7 (33.3)	
Histological type, No. (%)			0.967
ADC	13 (56.5)	12 (57.1)	
SCC	10 (43.5)	9 (42.9)	
TNM stage, No. (%)			0.989
IIIB	11 (47.8)	10 (47.6)	
IV	12 (52.2)	11 (52.4)	

DEB-BACE, drug-eluting beads bronchial artery chemoembolization; M ± SD, mean ± standard deviation; ECOG, Eastern Cooperative Oncology Group; ADC, adenomatous carcinoma; SCC, squamous cell carcinoma.

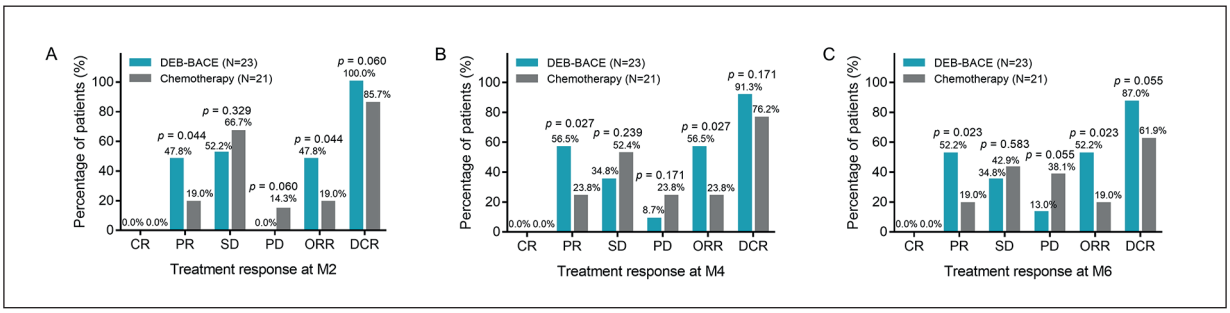

Figure 1. Treatment response at M2, M4 and M6 in two groups. Comparison of treatment response at M2 (**A**), M4 (**B**) and M6 (**C**) between DEB-BACE group and chemotherapy group. DEB-BACE, Drug-eluting bead bronchial arterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; M2, 2 months; M4, 4 months; M6, 6 months.

group compared with chemotherapy group, and the scores of nausea and vomiting (p =0.047) dyspnea (p <0.001), constipation (p =0.002) were decreased in DEB-BACE group compared with chemotherapy group. However, there was no difference in other QLQ-C30 item scores between two groups (all p >0.05). More detailed information of QLQ-C30 item scores in two groups was exhibited in Table II.

Comparison of Survival Profile

PFS was increased in DEB-BACE group compared with chemotherapy group (p =0.010) (Figure 2A). Furthermore, OS was also elevated in DEB-BACE group compared with chemotherapy group (Figure 2B). Further subgroup analysis indicated that in ADC subgroup, DEB-BACE presented increased PFS (p =0.015) (Figure 3A) and OS (p =0.005) (Figure 3B) compared with chemotherapy; however, in SCC subgroup, DEB-BACE and chemotherapy showed the similar PFS (p =0.110) (Figure 3C) and OS (p =0.099) (Figure 3D); furthermore, in TNM stage IIIB subgroup, DEB-BACE revealed higher PFS (p =0.024) (Figure 3E) and OS (p =0.003) (Figure 3F) compared with chemotherapy; meanwhile, in TNM stage IV subgroup, DEB-BACE exhibited similar PFS (p =0.077) (Figure 3G), but increased OS (p =0.044) (Figure 3H) compared to chemotherapy.

Table II. Comparison of QLQ-C30 score pretreatment and posttreatment between two groups.

QLQ-C30 Items	Pretreatment (M ± SD)			Posttreatment (at M2, M ± SD)		
	DEB-BACE (N = 23)	Chemotherapy (N = 21)	*p*-value	DEB-BACE (N = 23)	Chemotherapy (N = 21)	*p*-value
Global quality of life	41.9 ± 11.1	42.3 ± 9.4	0.914	47.4 ± 9.5	42.6 ± 9.5	0.108
Physical functioning	50.7 ± 9.3	51.8 ± 8.6	0.689	58.4 ± 9.6	51.3 ± 7.9	0.011
Role functioning	52.4 ± 8.4	52.9 ± 8.4	0.859	65.7 ± 8.0	57.7 ± 6.3	0.001
Emotional functioning	65.7 ± 7.4	65.3 ± 7.8	0.867	72.1 ± 6.9	66.1 ± 5.9	0.004
Cognitive functioning	67.8 ± 5.8	66.4 ± 6.1	0.446	74.6 ± 7.2	66.6 ± 5.4	< 0.001
Social functioning	58.8 ± 7.7	58.7 ± 6.7	0.961	65.8 ± 7.0	60.0 ± 6.4	0.006
Fatigue	53.5 ± 9.3	53.1 ± 8.2	0.875	46.4 ± 8.4	50.9 ± 7.2	0.064
Nausea and vomiting	26.8 ± 7.3	26.0 ± 5.9	0.706	21.6 ± 5.1	24.8 ± 5.3	0.047
Pain	45.1 ± 12.1	45.0 ± 11.2	0.982	38.1 ± 10.8	43.6 ± 8.6	0.068
Dyspnea	47.1 ± 4.7	46.8 ± 6.3	0.891	36.3 ± 4.0	42.7 ± 5.3	< 0.001
Insomnia	40.5 ± 13.1	40.5 ± 10.0	0.984	33.6 ± 10.4	39.0 ± 9.1	0.076
Appetite loss	45.2 ± 12.4	45.0 ± 10.8	0.970	37.8 ± 9.9	43.3 ± 10.5	0.085
Constipation	28.3 ± 6.9	28.1 ± 5.4	0.915	20.4 ± 4.8	25.3 ± 4.8	0.002
Diarrhea	17.2 ± 6.3	17.6 ± 5.1	0.802	13.8 ± 5.0	16.3 ± 4.3	0.084
Financial difficulties	46.2 ± 9.9	46.8 ± 6.5	0.822	48.5 ± 7.2	48.6 ± 11.3	0.969

QLQ-C30, quality of life Questionnaire–Core 30; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; M±SD, mean±standard deviation.

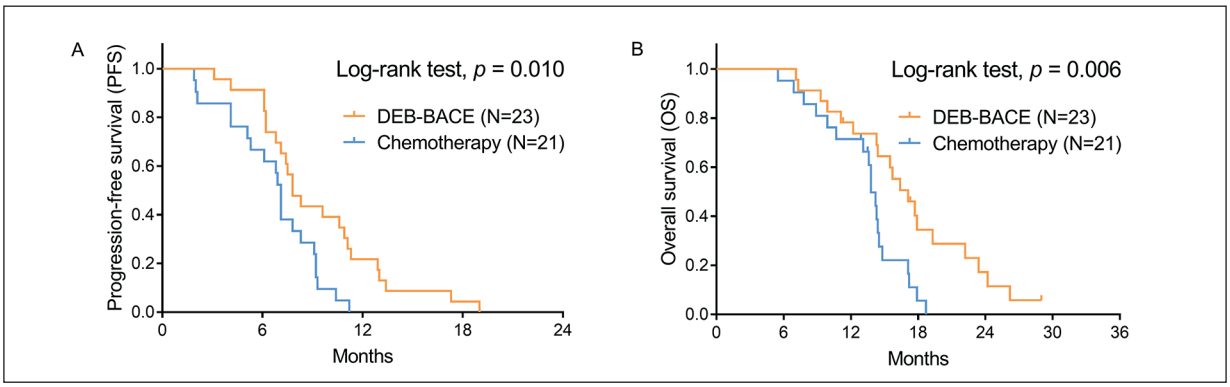

Figure 2. Survival profile in two groups. Comparison of PFS (**A**) and OS (**B**) between DEB-BACE group and chemotherapy group. DEB-BACE, Drug-eluting bead bronchial arterial chemoembolization; PFS, progression-free survival; OS, overall survival.

Factor Affecting ORR in Advanced NSCLC Patients

Univariate logistic regression analysis indicated that DEB-BACE (*vs.* chemotherapy) (OR=3.896, p =0.050) and histological type of ADC (*vs.* SCC) (OR=22.909, p =0.005) were associated with higher ORR at M2; however, ECOG score 2 (*vs.* 0/1) (OR=0.189, p =0.049) and TNM stage IV (*vs.* IIIB) were correlated with decreased ORR at M2 (Table III). Further multivariate logistic regression analysis revealed that DEB-BACE (*vs.* chemotherapy) (OR=20.851, p =0.026) and histological type of ADC (*vs.* SCC) (OR=73.269, p=0.006) were independent predictive factors for increased ORR at M2.

Factor Affecting Survival Profile in Advanced NSCLC Patients

Univariable Cox's proportional hazard regression analysis revealed that DEB-BACE (*vs.* chemotherapy) (HR=0.434, p =0.014) and histological type of ADC (*vs.* SCC) (HR=0.327, p =0.001) were associated with increased PFS; while age of >60 years (*vs.* ≤60 years) (HR=1.940, p =0.037), ECOG score 2 (*vs.* 0/1) (HR=2.204, p =0.017), TNM stage IV (*vs.* IIIB) (HR=2.423, p =0.005) were correlated with decreased PFS (Table IV). Further multivariate Cox's regression analysis exhibited that DEB-BACE (*vs.* chemotherapy) (HR=0.235, p <0.001) and histological type of ADC (*vs.* SCC) (HR=0.175, p <0.001) were independent predictive factors for increased PFS, while TNM stage IV (*vs.* IIIB) (HR=2.333, p =0.021) was an independent predictive factor for decreased PFS.

Univariable Cox's proportional hazard regression analysis demonstrated that DEB-BACE (*vs.* chemotherapy) (HR=0.386, p =0.009) and histological type of ADC (*vs.* SCC) (HR=0.220, p <0.001) were correlated with increased OS, while ECOG score 2 (*vs.* 0/1) (HR=2.580, p =0008) and TNM stage IV (*vs.* IIIB) (HR=4.236, p <0.001) were associated with decreased OS (Table V). Further multivariate Cox's regression analysis elucidated that DEB-BACE (*vs.* chemotherapy) (HR=0.098, p <0.001) and histological type of ADC (*vs.* SCC) (HR=0.056, p <0.001) were independent predictive factors for increased OS, however, age >60 years (*vs.*≤60 years) (HR=2.424, p =0.043) and TNM stage IV (*vs.* IIIB) (HR=9.123, p <0.001) were independent predictive factors for decreased OS.

The Safety Profile of Adverse Event

All patients in two groups presented no serious adverse events such as spinal damage, pulmonary embolism, cerebrovascular adverse events, and venous thrombosis of the lower limb, and no difference of serious adverse events was observed between two groups. Regarding the adverse events in DEB-BACE group, the common adverse events included fever, chest pain, chest distress, myelosuppression, gastrointestinal reaction, hemoptysis, rash, which were mild and occurred on the day of DEB-BACE or on the second day after DEB-BACE treatment. Among all the adverse treatment, the incidence of chest pain and distress were the highest, followed by the incidence of fever, and the highest temperature of patient was about 38-39°C. The majority of adverse events were relieved by themselves or through appropriate management (nonsteroidal anti-inflammation drugs).

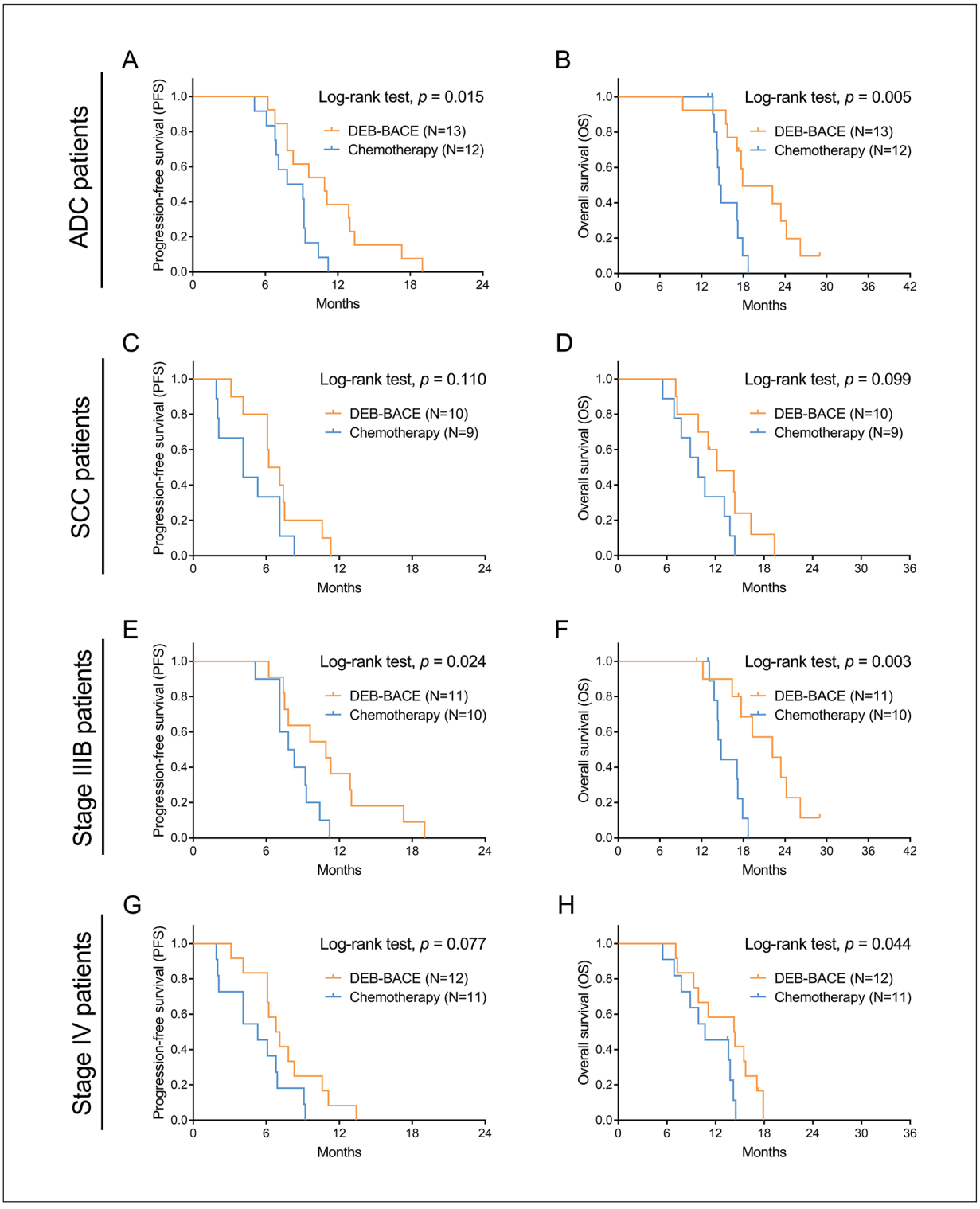

Figure 3. Survival profile in subgroup analysis. Comparison of PFS (**A**) and OS (**B**) between patients received DEB-BACE and those received chemotherapy in subgroup of ADC patients. Comparison of PFS (**C**) and OS (**D**) between patients received DEB-BACE and those received chemotherapy in subgroup of SCC patients. Comparison of PFS (**E**) and OS (**F**) between patients received DEB-BACE and patients received chemotherapy in subgroup of stage IIIB patients. Comparison of PFS (**G**) and OS (**H**) between patients received DEB-BACE and those received chemotherapy in subgroup of stage IV patients. DEB-BACE, Drug-eluting bead bronchial arterial chemoembolization; PFS, progression-free survival; OS, overall survival; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

Table III. Factors affecting ORR at M2.

Parameters	Univariate logistic regression				Multivariate logistic regression			
			95% CI				95% CI	
	p-value	OR	Lower	Higher	*p*-value	OR	Lower	Higher
Treatment								
Chemotherapy	Ref				Ref			
DEB-BACE	0.050	3.896	0.998	15.213	0.026	20.851	1.429	304.308
Age								
≤ 60 years	Ref				Ref			
> 60 years	0.245	0.471	0.132	1.676	0.659	0.642	0.090	4.597
Gender								
Female	Ref				Ref			
Male	0.462	0.622	0.176	2.202	0.538	0.363	0.014	9.107
History of smoke								
No	Ref				Ref			
Yes	0.908	0.929	0.266	3.244	0.578	2.460	0.104	58.454
ECOG score								
0/1	Ref				Ref			
2	0.049	0.189	0.036	0.995	0.399	0.342	0.028	4.144
Histological type								
SCC	Ref				Ref			
ADC	0.005	22.909	2.634	199.241	0.006	73.269	3.330	1612.093
TNM stage								
IIIB	Ref				Ref			
IV	0.019	0.191	0.048	0.758	0.076	0.106	0.009	1.262

ORR, objective response rate; OR, odds ratio; CI, confidence interval; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; ECOG, Eastern Cooperative Oncology Group; ADC, adenomatous carcinoma; SCC, squamous cell carcinoma.

Table IV. Factors affecting PFS.

Parameters	Univariate Cox's regression				Multivariate Cox's regression			
			95% CI				95% CI	
	p-value	OR	Lower	Higher	*p*-value	OR	Lower	Higher
Treatment								
Chemotherapy	Ref				Ref			
DEB-BACE	0.014	0.434	0.224	0.843	< 0.001	0.235	0.109	0.506
Age								
≤ 60 years	Ref				Ref			
> 60 years	0.037	1.940	1.040	3.618	0.070	1.969	0.946	4.096
Gender								
Female	Ref				Ref			
Male	0.796	1.083	0.593	1.978	0.817	0.910	0.410	2.020
History of smoke								
No	Ref				Ref			
Yes	0.607	1.176	0.634	2.181	0.438	1.373	0.616	3.060
ECOG score								
0/1	Ref				Ref			
2	0.017	2.204	1.150	4.223	0.136	1.750	0.838	3.653
Histological type								
SCC	Ref				Ref			
ADC	0.001	0.327	0.171	0.627	< 0.001	0.175	0.079	0.386
TNM stage								
IIIB	Ref				Ref			
IV	0.005	2.423	1.301	4.512	0.021	2.333	1.133	4.804

PFS, progression-free survival; HR, hazards ratio; CI, confidence interval; Ref, reference; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; ECOG, Eastern Cooperative Oncology Group; ADC, adenomatous carcinoma; SCC, squamous cell carcinoma.

Table V. Factors affecting OS.

Parameters	Univariate Cox's regression				Multivariate Cox's regression			
			95% CI				95% CI	
	p-value	OR	Lower	Higher	*p*-value	OR	Lower	Higher
Treatment								
Chemotherapy	Ref				Ref			
DEB-BACE	0.009	0.386	0.190	0.786	< 0.001	0.098	0.037	0.262
Age								
≤ 60 years	Ref				Ref			
> 60 years	0.056	1.962	0.983	3.917	0.043	2.424	1.029	5.709
Gender								
Female	Ref				Ref			
Male	0.173	1.568	0.821	2.995	0.135	2.014	0.804	5.043
History of smoke								
No	Ref				Ref			
Yes	0.148	1.630	0.841	3.159	0.307	1.558	0.665	3.652
ECOG score								
0/1	Ref				Ref			
2	0.008	2.580	1.278	5.211	0.624	1.265	0.495	3.231
Histological type								
SCC	Ref				Ref			
ADC	< 0.001	0.220	0.108	0.448	< 0.001	0.056	0.018	0.168
TNM stage								
IIIB	Ref				Ref			
IV	< 0.001	4.236	1.973	9.096	< 0.001	9.123	3.129	26.603

OS, overall survival; HR, hazards ratio; CI, confidence interval; Ref, reference; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; ECOG, Eastern Cooperative Oncology Group; ADC, adenomatous carcinoma; SCC, squamous cell carcinoma.

One Typical Case Treated by DEB-BACE

Before the treatment of DEB-BACE, a series of medical examinations were performed. Left bronchial artery angiography observed the tumor with abundant feeding arteries (Figure 4A); furthermore, left Intercostal artery (4-5) arteriography showed the staining of the regional pleura (Figure 4B) and right bronchial artery with normal shape originated from the intercostal artery (Figure 4C); meanwhile, chest transverse computed tomography (CT) revealed that a pleura-attached mass shadow at the left upper lobe with a maximum diameter of approximate 7 cm (Figure 4E, 4G); additionally, positron emission tomography (PET)-CT showed the regional visceral pleura with hypermetabolic activities, further verifying that tumor at the left upper lobe invaded regional visceral pleura (Figure 4I, 4K, 4M). Therefore, considering the physical performance and general condition, DEB-BACE treatment was conducted. After embolization at the left bronchial artery, arterial angiography did not show tumor-feeding arteries, suggesting the successful implantation of embolization (Figure 4D). At one-month post-treatment, another transverse CT scan was conducted, which revealed that the tumor at the periphery of the left upper lobe regressed with a maximum diameter of approximately 5 cm (Figure 4F, 4H). Furthermore, at 6 months post-treatment, the follow-up PET-CT scan observed that tumor further greatly reduced in size, and visceral pleura showed no sign of hypermetabolic activities (Figure 4J, 4L, 4N).

Discussion

In the present study, we found that in advanced NSCLC patients, (1) DEB-BACE treatment showed higher treatment response at M2, M4, and M6 post initial treatment compared with chemotherapy, which was further verified by regression analysis. (2) DEB-BACE treatment presented with increased ability in prolonging survival compared with chemotherapy, which was further supported by subgroup analysis and regression analysis. (3) Patients who received DEB-BACE exhibited better QoL compared with patients who received chemotherapy. (4) Patients who received DEB-BACE treatment presented

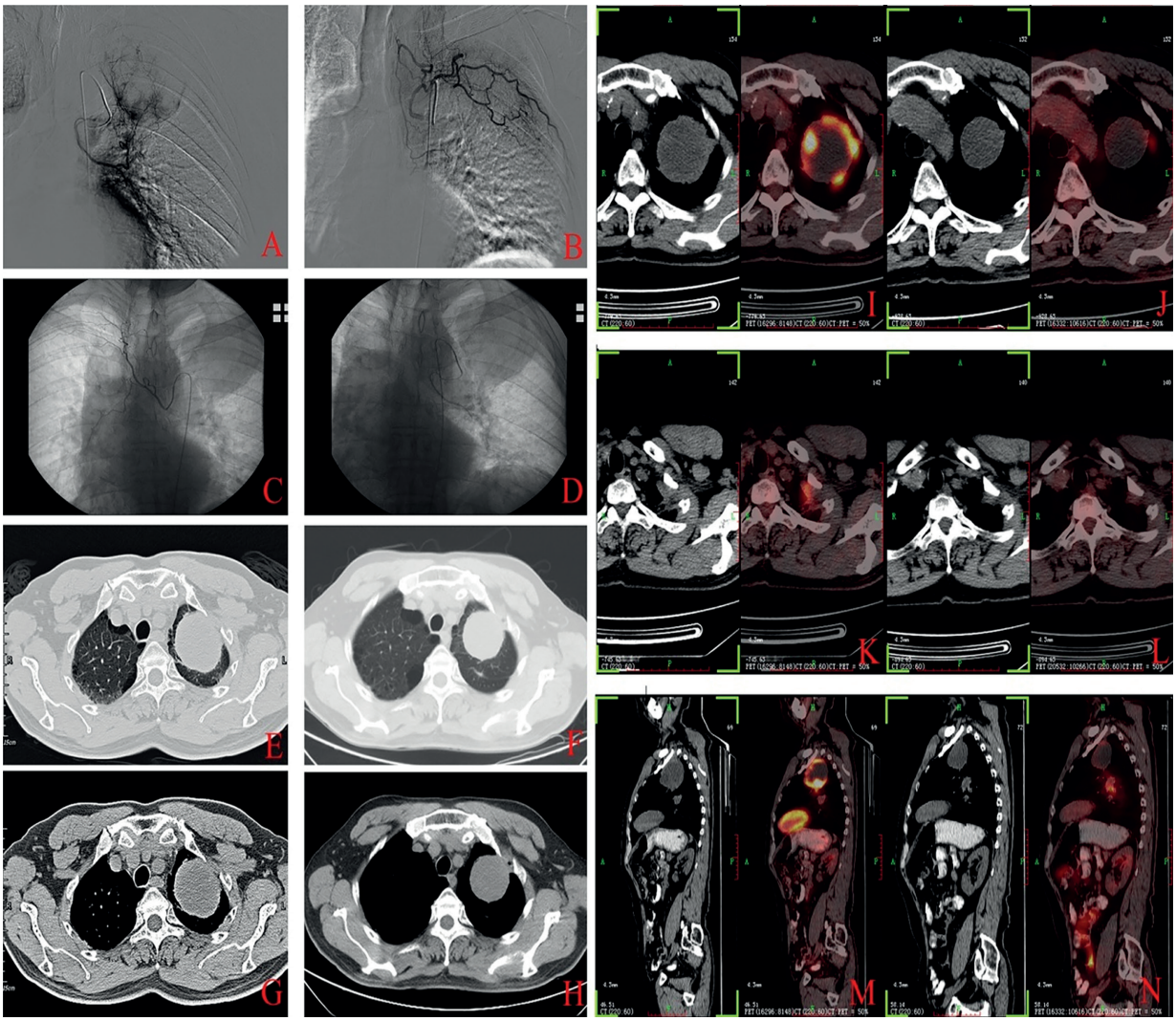

Figure 4. Case report. Tumor-feeding arteries by pretreatment left bronchial artery angiography (**A**). The staining of the regional pleura by left Intercostal artery (4-5) arteriography (**B**). Before embolization, right bronchial artery originating from the intercostal artery (**C**). After embolization, disappeared tumor-feeding arteries at the left bronchial artery (**D**). A pleura-attached mass shadow at the periphery of left upper lobe, with maximum diameter of approximate 7 cm by pretreatment chest CT (**E, G**); The reduction of tumor size at the periphery of left upper lobe with the maximum diameter of approximately 5 cm by post-treatment chest CT (**F, H**). Tumor invaded regional visceral pleura at the left upper lobe and presented with effective metabolism by pretreatment PET-CT (**I, K, M**). Decreased tumor size at the periphery of left upper lobe without metabolic activity by post-treatment PET-CT (**J, L, N**). CT, computed tomography; PET, positron emission tomography.

no difference of serious adverse events compared with those who received chemotherapy, and majority of adverse events were mild.

The application of BACE in NSCLC has been reported in some studies[7-9]. Chen et al[8] indicate that after conventional BACE treatment in 32 advanced NSCLC patients, the ORR was 40.6%, and DCR was 59.5% at 6 months, and their median PFS and OS are 8.2 months and 544 days, respectively. Studies exploring DEB-BACE in NSCLC patients is rarely reported, but only one retrospective observational study reveals that DEB-BACE exhibits 50.0% ORR and 66.7% DCR at 6 months after DEB-BACE treatment, and the median PFS and OS are 8.0 months (25^{th}-75^{th} quantiles: 4-23 months) and 16.5 months (25^{th}-75^{th} quantiles: 7-23 months) respectively, suggesting the potential of DEB-BACE as a therapeutic option for NSCLC patients who are ineligible to standard treatment[7]. However, the evidence to compare the treatment

efficacy between DEB-BACE and standard chemotherapy for the treatment of advanced NSCLC remained blank, which was investigated in the present research.

In the present study, advanced NSCLC patients treated by DEB-BACE achieved higher ORR and showed an increased tendency of DCR compared with those who received chemotherapy treatment at 2, 4, 6 months post-treatment. Besides, further logistic regression analysis also verified this finding, which implied that DEB-BACE had short-term therapeutic efficacy in treating advanced NSCLC patients. The possible reasons might include that (1) compared with systematic chemotherapy, anti-tumor drug release by DEB-BACE allowed for more selective and higher concentration delivery of chemotherapeutic drugs to mass lesions, which led to localized and directed intra-tumoral concentration and drug retention duration in NSCLC, thereby further increased treatment response[15]. (2) In addition, except for the tumor-selective drug delivery, DEB-BACE had extra embolization capacity compared with chemotherapy, which resulted to the synergistic effect of regional cytotoxic activity and ischemia at tumor site, thereby improved the treatment response in advanced NSCLC patients[7,15].

Subsequently, the comparison of survival profile and further subgroup analysis disclosed that DEB-BACE (*vs.* chemotherapy) was associated with increased PFS and OS independent of TNM stage, which was also supported by Cox's proportional hazard regression analysis. This suggested that DEB-BACE had long-term therapeutic efficacy for the treatment of advanced NSCLC. The possible reasons were: (1) DEB-BACE was regarded as an effective chemotherapeutic delivery, benefiting from more sustained drug concentration and localized drug; therefore, DEB-BACE presented a more favorable survival profile compared with chemotherapy[10,11,15]. (2) In addition, being consistent with the prior study, the superior treatment response of DEB-BACE might prolong the survival of advanced NSCLC patients[16].

QoL is considered as important as survival in patients with advanced NSCLC[17]. In this study, we observed that patients receiving DEB-BACE had increased overall QoL regarding higher scores in functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning) as well as decreased scores of symptom scales (nausea and vomiting) and single-item (dyspnea, constipation) compared to patients receiving chemotherapy. Of note, the difference was remarkable on the score of dyspnea, which indicated less decline in lung function by DEB-BACE treatment compared to chemotherapy. Furthermore, according to the previous evidence[18], patients who suffer from dyspnea show higher risk of worse prognosis than those without dyspnea, the superiority of DEB-BACE treatment over chemotherapy in improving prognosis of advanced NSCLC patients is shown. The possible reasons might include that (1) DEB-BACE had increased therapeutic efficacy compared with chemotherapy, therefore patients receiving DEB-BACE presented better clinical presentation, which was reflected in the aspect of functioning improvement in advanced NSCLC patients[7]. (2) Compared with conventional intravenous chemotherapy, DEB-BACE was supposed to reduce the peripheral concentration of drug, further decreasing the risk of systemic toxicity in patients with advanced NSCLC; therefore, patients receiving DBE-BACE treatment had less gastrointestinal reaction compared with those receiving chemotherapy[15]. (3) In terms of the similar scores in some items, it might be due to the fact that BACE commonly caused death to cancer cells from lack of oxygen and nutrients, which might lead to inflammation and further stimulate the occurrence of the post-embolization syndrome (including fatigue, pain, insomnia, appetite loss, diarrhea)[19]. Meanwhile, these symptoms were also very commonly caused by chemotherapeutic agents (pemetrexed/ gemcitabine)[6,20]. Hence, scores of fatigues, pain, insomnia, appetite loss and diarrhea were similar between patients who received DEB-BACE and patients who received chemotherapy.

In addition, regarding the safety profile, no serious adverse events occurred during the study and no difference of serious adverse events was observed between patients receiving DEB-BACE and patients receiving chemotherapy. Notably, for DEB-BACE, the majority of adverse events were post-chemotherapy and post-embolization syndromes, which were mild and could be relieved via nonsteroidal anti-inflammation drugs, suggesting the tolerable safety profile of DEB-BACE for treatment of advanced NSCLC[7,8].

However, we acknowledged that the present study still had some limitations. Firstly, this study was a retrospective cohort study from a single center; therefore, selection bias and confounding factors might exist, which might lead to lower

statistical power. Secondly, DEB-BACE was a novel therapeutic approach for advanced NSCLC, and the sample size of patients receiving DEB-BACE was relatively small in this study; thus, more patients were needed to validate the results. Thirdly, some confounders, such as the distinctions in the operation skills of surgeons, were not included in the analysis.

Conclusions

Our study is the first study indicating that DEB-BACE presents favorable treatment response, prolonged survival, improved QoL, and tolerable safety compared with chemotherapy in advanced NSCLC patients, which exhibits the preference of DEB-BACE for the advanced NSCLC treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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