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Efficacy and safety of bevacizumab for patients with advanced non-small cell lung cancer

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Abstract: **To observe the efficacy and safety of bevacizumab in the treatment of advanced non-small cell lung cancer (NSCLC). We retrospectively analyzed 36 patients of Stage IV non-squamous non-small cell lung cancer from March 2015 to December 2016. All patients were treated with Bevacizumab combined with Pemetrexed ± Platinum. The efficacy and adverse reactions were observed and followed up. In 36 patients, 10 patients (27.8%) had partial response, 22 patients (61.1%) had stable disease and 4 (11.1%) had progressive disease. The objective response rate was 27.8% and the disease control rate was 88.9%. The median progression-free survival time was 7.3 months and the median overall survival time was 13.1 months. The most common bevacizumab-related adverse events were proteinuria, hemorrhage and hypertension. Most adverse events were relieved after symptomatic treatment, and severe adverse reactions (grade 3 or above) were rare. Bevacizumab has definite therapeutic effect for advanced NSCLC patients and most adverse reactions could be tolerated.**

Keywords: Bevacizumab; Non-small cell lung cancer; Adverse event

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1. Introduction

Lung cancer is one of the highest incidence of cancer in the world, especially NSCLC. Current effect of chemotherapy seems to have reached the bottleneck state [1]. Early in 1971, Folkman et al. found that neovascularization played a key role in growth, development and metastasis of tumors. Since then, inhibition of tumor angiogenesis became new focus of cancer treatment. The researchers found out that the vascular endothelial growth factor (VEGF) is the main medium of various influencing factors in the process of vascular abnormalities. The combination of VEGF and VEGFR promotes the proliferation and migration of abnormal tumor vascular endothelial cells and increases the permeability of abnormal blood vessels, while anti-angiogenic agents play a role in pruning and normalizing neovascularization [2]. Bevacizumab as a humanized anti-VEGF drug is the first anti-angiogenic drug that approved by the FDA for first-line treatment of advanced NSCLC.

Bevacizumab combined with standard regimen has been shown to improve patient survival. Phase III BEYOND trial studied the efficacy of bevacizumab in combination with paclitaxel in initial treatment of NSCLC. The median PFS was 9.2 months, the ORR was 54%, and the median OS was 24.3 months [3]. A multicenter Phase II trial selected 36 patients with NSCLC to give pemetrexed/oxaliplatin combined with bevacizumab for second-line therapy. The median PFS was 5.8 months and the median OS was 12.5 months [4]. These studies suggest that the addition of bevacizumab in chemotherapy could increase the overall survival time of the patients with advanced NSCLC. Currently, paclitaxel or pemetrexed combined with bevacizumab is the most frequently used regimen for both first and second lines. The combination of bevacizumab and chemotherapy undoubtedly prolongs OS and PFS in advanced non-squamous NSCLC, compared with chemotherapy alone. However, whether the maintenance treatment with bevacizumab can improve patient survival still requires further study and the initial treatment and retreatment of patients (including second-line and above) still need more research to compare the efficacy. In this paper, patients with advanced NSCLC treated with pemetrexed combined with bevacizumab were retrospectively analyzed.

2. Materials and Methods

2.1. Patients

We collected 36 cases with pathological diagnosis of Stage IV non-squamous non-small cell lung cancer between March 2015 to December 2016 from the Department of oncology, Affiliated Hospital of Qingdao University. All patients were diagnosed by pathology and/or cytology. Each person had a lesion that could be evaluated or measured and their expected survival time is equal to or more than 3 months. They all had an ECOG PS of 0 to 2 and the blood parameters and cardiac function were ensured to be normal before treatment.

2.2. Treatment

Of the 36 patients, 21 patients received first-line treatment and 15 patients received second-line and above treatment. They were all treated with intravenous infusion of bevacizumab (7.5mg/kg) plus

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pemetrexed (500mg/m²) in combination with platinum administered every 3 weeks and at least one cycle of therapy. After platinum-based chemotherapy, 19 patients continued to receive maintenance treatment with bevacizumab combined with pemetrexed. Maintenance patients were treated with intravenous infusion of bevacizumab (7.5mg/kg) in combination with pemetrexed (500mg/m²) administered every 3 weeks. In the study, conventional applications of dexamethasone, folic acid and vitamin B12 were administered prior to each cycle of treatment.

2.3. Assessments

Tumor response assessment was performed by computer tomography, according to the response evaluation criteria in solid tumors (RECIST) criteria. The results of the evaluation include complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). The objective response rate (ORR) was equal to the sum of CR and PR as a percentage of the total number of cases, the disease control rate (DCR) was equal to the sum of CR, PR and SD as a percentage of the total number of cases. Progression free survival (PFS) was defined as the time from initiation of treatment to disease progression or death. Overall survival (OS) was defined as the time from the start of treatment to the death of the patient or the end of the follow-up. Toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0.

2.4. Statistical analysis

Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) software 23.0. PFS and OS were analyzed by Kaplan-Meier method and tested by Log-rank method. The data between groups were compared by $\chi 2$ test and the difference was statistically significant ($P<0.05$).

Table 1 Baseline characteristics

Characteristics	Number of Patients (n = 36)	%
Gender		
Male	23	63.9
Female	13	36.1
Age (Year)		
≥60	20	55.6
＜60	16	44.4
ECOG PS		
0-1	24	66.7
2	12	33.3
History of Hypertension		
Yes	10	27.8
No	26	72.2
History Of Hemoptysis		
Yes	6	16.7
No	30	83.3
Brain Metastases		
Yes	6	16.7
No	30	83.3

ECOG PS: Eastern Cooperative Oncology Group performance status.

3. Results

3.1. Patients' characteristics

36 patients were enrolled in this study. The last follow-up time was December 2016. No patient was lost and all of them could be evaluated. Among all the patients, 20 patients (55.6%) were more than 60 years of age (median 57 years; range 28–68 years) and 23 patients (63.9%) were male. 24 patients (66.7%) had an ECOG PS of 0-1 and 12 patients (33.3%) had a PS of 2. The clinical characteristics of all patients are listed in Table 1.

3.2. Efficacy

For all patients treated, the median treatment regimen was 5 (range 2-22). Among the 36 patients, the first assessment response (after 2 cycles) was 10 patients with PR (27.8%), 22 patients with SD (61.1%) and 4 patients with PD (11.1%). The ORR was 27.8% and DCR was 88.9%. The Kaplan-Meier curves for PFS and OS are shown in Figure 1. The median PFS was 7.3 months, 95% confidence interval (CI) was 5.9-8.7 months, and the median OS was 13.1 months (95%CI, 11.8-14.4 months).

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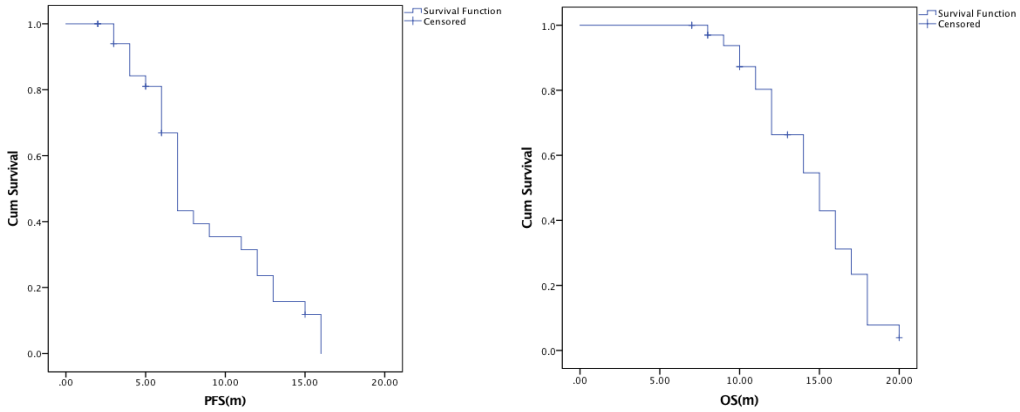


Figure 1. Progression-free and overall survival curves for 36 patients with non-small cell lung cancer.

The median number of cycle in the initial treatments was 9 (range 3-22) and in the retreatments was 4 (range 2-10). Of the 21 patients who received first-line treatment, there were 6 of PR, 13 of SD and 2 of PD. The ORR was 28.6% and DCR was 90.6%. The median PFS was 9.0 months (95%CI, 6.9-10.0 months) and the median OS was 14.5 months (95% CI, 12.7-16.3 months). Of the 15 patients who had previously received treatment, there were 4 of PR, 9 of SD, 2 of PD. The ORR was 26.7% and DCR was 86.7%. The median PFS was 5.0 months (95%CI, 3.8-6.2 months) and the median OS was 11.1 months (95%CI, 9.6-12.6 months). Statistical analysis showed that PFS in patients with first-line therapy had a trend of better than retreatment (P=0.054) and the former OS was significantly better than the latter (p<0.05, Table 2).

52.8% (19/36) of the patients received maintenance treatment with bevacizumab combined with pemetrexed and the median number of treatment cycles was 6 (range 1-17). Among the patients who continued to receive maintenance therapy, including 7 of PR, 12 of SD and no PD. ORR and DCR were 36.8% and 100.0%, respectively. The median PFS was 9.8 months (95%CI, 7.8-11.8), the median OS was 15.4 months (95%CI, 14.0-16.7 months). Of the patients who did not continue to receive maintenance therapy, including 3 of PR, 10 of SD and 4 of PD. The ORR and DCR were 17.6% and 76.5%, respectively. The median PFS was 4.5 months (95%CI, 3.5-5.5 months), the median OS was 10.5 months (95% CI, 8.9-12.2 months). The former DCR, PFS and OS were significantly better than the latter, and the difference was significant (P<0.05, Figure 2 and Table 2).

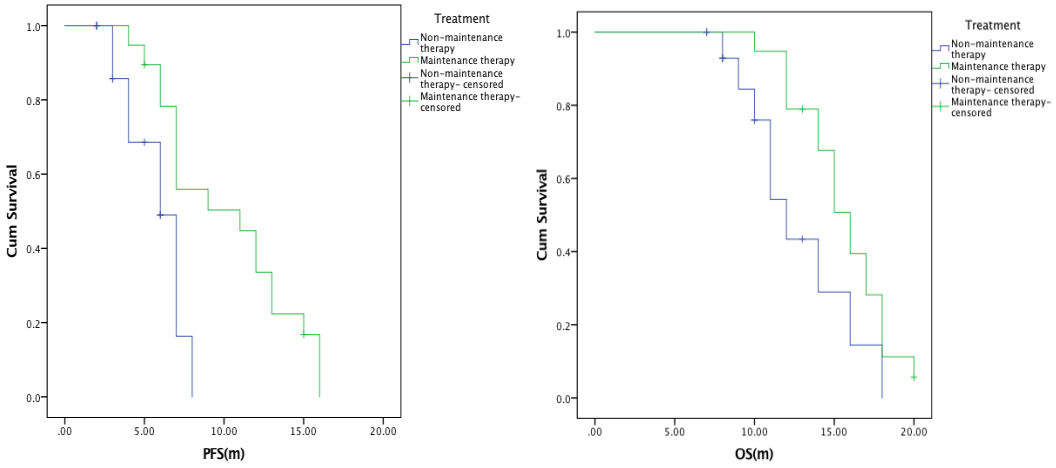


Figure 2. Survival curves of PFS and OS with maintenance and no maintenance therapy.

There were 16 patients with EGFR mutations, 14 patients with EGFR wild type, and 6 patients without EGFR detection for economic reasons. Patients with EGFR mutations had a DCR of 93.8%, a median PFS of 8.4 months (95%CI, 5.9-11.0 months) and a median OS of 15.8 months (95%CI, 14.2-17.4 months). EGFR wild-type patients had a DCR of 78.6%, a median PFS of 6.4 months (95% CI, 4.0-8.7 months) and a median OS of 10.4 months (95%CI, 8.4-12.3 months). Compared with patients with

wild-type EGFR, the mutant patient's OS was much longer (P<0.05, Table 2).

Table 2 Effect analysis of subgroups

Group	Patients (n = 36)	DCR(%)	PFS(month, 95%CI)	OS(month, 95%CI)
Treatment				
Initial	21(58.3)	90.6	9.0(6.9-11.0)	14.5(12.7-16.3)
Repeated	15(41.7)	86.7	5.0(3.8-6.2)	11.1(9.6-12.6)
p		0.720	0.054	0.047
Maintenance Therapy				
Yes	19(52.8)	100.0	9.8(7.8-11.8)	15.4(14.0-16.7)
No	17(47.2)	76.5	4.5(3.5-5.5)	10.5(8.9-12.2)
p		0.025	0.007	0.045
EGFR Status				
unknown	6(16.7)			
Mutant-type	16(44.4)	93.8	8.4(5.9-11.0)	15.8(14.2-17.4)
Wild-type	14(38.9)	78.6	6.4(4.0-8.7)	10.4(8.4-12.3)
p		0.222	0.967	0.008

DCR: the disease control rate; PFS: Progression free survival time; OS: Overall survival time.

3.3. Toxicity

The adverse reaction data is shown in Table 3. The most common adverse reactions are chemotherapy-related, and most of them are grade 1-2 that can be improved after symptomatic treatment. The side effects caused by bevacizumab were mainly proteinuria (22.2%), diarrhea (11.1%), hemorrhage (16.7%) and hypertension (13.9%). 3 cases of epistaxis, 2 cases of skin and mucous membrane bleeding and 1 case of gastrointestinal bleeding were observed in all bleeding patients. These patients did not continue bleeding after being given symptomatic treatment.

4. Discussion

Several previous studies have confirmed the anti-tumor effect of bevacizumab in advanced NSCLC patients. Phase III ECOG clinical study randomly assigned 878 patients to the combination therapy group and the separate chemotherapy group. The results showed a significant increase in OS (12.3 vs. 10.3 months) and PFS (6.2 vs. 4.5 months) in the combined treatment group. The ORR was higher than that of the chemotherapy alone group (35% vs. 15%). It showed that bevacizumab combined with paclitaxel plus platinum regimen had a significant survival benefit in the treatment of patients with NSCLC, and more bleeding events (4.4% vs. 0.7%) were observed in the combined group than in the control group [5]. In our study, the median PFS and OS of all patients were 7.3 (5.9-8.7) and 13.1 (11.8-14.4) months, and ORR and DCR were 27.8% and 88.9%, respectively. Our results of PFS and OS are better than those in the ECOG trial, but not the ORR. The results are limited by the total number of patients, therefore, any conclusions should be taken with caution.

In phase II clinical study conducted by Yokoi et al., patients with advanced NSCLC received first-line chemotherapy with pemetrexed combined with bevacizumab. Median PFS and OS reached 8.6 months and 18.6 months, respectively, suggesting that this treatment regimen may provide more benefits for the Asian population [6]. Ding et al. studied the role of pemetrexed in combination with bevacizumab in second-line therapy for advanced NSCLC. Twenty-eight patients (84.8%) received chemotherapy with pemetrexed. The median PFS was 4.4 months (95% CI, 2.6-6.1 months) and the median OS was 15.8 months (95%CI, 10.5-21.2 months), toxicity is similar to the historical data of the two drugs [7]. These studies showed that the combination of bevacizumab and pemetrexed is effective and tolerant in patients with advanced NSCLC. Similar to above results, the median PFS of the first-line treatments was 9.0 months and the second and subsequent-line therapies was 5.0 months. The median OS was 14.5 months and 11.1 months respectively, which was lower than other studies. Considering OS is less than other studies because the study's follow-up time was not long enough. This study confirmed that bevacizumab combined with pemetrexed has a definite improvement in PFS for both first-line therapy and retreatment of advanced NSCLC. PFS of first-line treatment was superior to those in retreatment (9.0 vs. 5.0 months) and OS was significantly longer (14.5 vs. 11.1 months). This suggests that pemetrexed combined with platinum and bevacizumab for the first-line treatment is superior to the second and subsequent treatment of patients with advanced NSCLC.

A randomized study of AVAPERL evaluated the efficacy of bevacizumab/pemetrexed maintenance therapy and the efficacy of bevacizumab alone. The study showed that the overall survival rate was superior to the non-progression of advanced NSCLC

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patients with significant PFS benefit (10.2 months vs. 6.6 months) compared with the use of bevacizumab alone, with a hazard ratio of 0.57 [8]. Karayama randomized patients with advanced ns-NSCLC to be treated with pemetrexed/bevacizumab or pemetrexed for maintenance. The results showed that the average 1-year PFS was 43.9% in the combined maintenance group and 35.2% in the pemetrexed group, the difference was not significant (p=0.433)[9]. It can be seen that maintenance therapy of pemetrexed and bevacizumab in patients with advanced ns-NSCLC is feasible, but whether can improve survival requires further validation. In our study, compared with patients without maintenance therapy, the DCR of maintenance patients was significantly superior to the latter (100% vs. 76.5%) and PFS (9.8 vs. 4.5 months) and OS (15.4 vs. 10.5 months) were significantly improved. The result of PFS is similar to AVAPERL trials. It can be seen that continuous application of bevacizumab could effectively improve the patient survival period in the treatment of patients with advanced NSCLC in the study.

A large phase IV SAIL (n=2212) clinical trial evaluated the safety of standard chemotherapy combination with bevacizumab in Chinese patients [10]. The results of subgroup analysis in Chinese patients showed a lower incidence of grade 3 and above adverse events (<9%). The bleeding of bevacizumab and chemotherapy related clinical events analysis showed that bleeding adverse events occurred in 38.2% patients (3.6% for more than grade 3). Pulmonary hemorrhage (more than grade 3) and central nervous system bleeding events were observed in 0.7% and 0.1% of the patients. Most bleeding events (88.6%) were resolved or improved. 10.2% persisted, and 1.3% resulted in death [11]. The most common adverse events in the course of this study were chemotherapy-related (mostly grade 1-2). And the incidence of hypertension, bleeding, and diarrhea in bevacizumab-resistant adverse events were similar to those previous studies. There were no new safety signals. Patients with a history of high blood pressure had no correlation with hypertension in the course of treatment due to small sample size. 5.6% of patients had bleeding events (grade 3 and above). All bleeding patients were improved after treatment, and there was no sustained bleeding. Four of the six bleeding patients had a history of hemoptysis. It is suggested that patients with previous hemoptysis should be given high attention during the treatment of bevacizumab. Six patients with brain metastases did not experience cerebral hemorrhage in the treatment. This is considered to be tolerated by bevacizumab in the treatment of advanced NSCLC patients with brain metastases.

There was no significant difference in PFS between EGFR mutation and wild-type patients, but OS was significantly prolonged (15.8 vs. 10.4 months). But there was a bias because of the small sample size and 6 patients who did not have EGFR test for economic reasons.

Table 3 Treatment-related adverse events

Adverse Events	Grade1-2	Grade3-4	Patients (n = 36) (%)
Chemotherapy Related			
Leukopenia	14(38.9)	4(11.1)	18(50.0)
Neutropenia	16(44.4)	11(30.6)	27(75.0)
Thrombopeny	7(19.4)	6(16.7)	13(36.1)
Anemia	23(63.9)	4(11.1)	27(75.0)
Hepatic Dysfunction	16(44.4)	0(0)	16(44.4)
Renal Dysfunction	6(16.7)	0(0)	6(16.7)
Vomiting	19(52.8)	3(8.3)	22(61.1)
Bevacizumab Related			
Proteinuria	8(22.2)	0(0)	8(22.2)
Diarrhea	4(11.1)	0(0)	4(11.1)
Hypertension	5(13.9)	0(0)	5(13.9)
Hemorrhage	4(11.1)	2(5.6)	6(16.7)

5. Conclusion

In the treatment of advanced NSCLC in this study, bevacizumab combined with first-line or second-line and above regimen can improve the efficacy of chemotherapy in patients and especially for patients with maintenance therapy. Bevacizumab is the first drug to be shown to improve the survival of patients with advanced NSCLC and is currently considered an important component in the treatment of advanced NSCLC. In view of cost-effectiveness, the application of bevacizumab in clinical practice is not extensive. In the study, the sample size is insufficient and further follow-up time is required, and larger trials are needed to determine the more adverse reactions that should be cautious in the benefit population and in the application.

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