Original Article
Clinical efficacy of bevacizumab combined with chemotherapy in the treatment of advanced non-squamous non-small cell lung cancer

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Abstract: Objective: To determine the efficacy of bevacizumab in combination with chemotherapy in the treatment of advanced non-squamous non-small cell lung cancer (NSNSCLC). Methods: A retrospective study was conducted in 72 patients with advanced NSNSCLC. Depending on whether or not bevacizumab was used in combination with chemotherapy, the patients were divided into an observation group and control group with 36 cases each. The observation group was further divided into combination group (23 cases) and single drug group (13 cases) based on whether or not bevacizumab was used in the maintenance therapy. The efficacy and adverse effects of different therapies were compared. Results: In terms of efficacy, the objective remission rate of the observation group was significantly better than that of the control group (P<0.05). The five-year progression-free survival (PFS) of the observation group was also significantly longer than that of the control group (P<0.05). Specifically, the PFS of the maintenance therapy in the combination group was significantly longer than that in the single drug group (P<0.05). In terms of adverse effects, the observation group had a significantly higher incidence of hypertension than the control group (P<0.05). Conclusion: In this study, bevacizumab was efficient and safe in the treatment of advanced NSNSCLC which makes it a notable drug for clinical applications and further research.

Keywords: Non-squamous non-small cell lung cancer, bevacizumab, chemotherapy, efficacy

Introduction

Lung cancer, a disease with high incidence, has been greatly undermining human health. Globally, it is estimated that there are about 1.8 million new cases (13.3% of the new tumor cases) and 1.6 million mortality cases (19.4% of all mortality cases) of lung cancer annually, ranking it first in tumor morbidity and mortality worldwide. In 2013, the National Cancer Center of China reported that there were 733,000 new cases with 591,000 deaths from lung cancer which comprises 44.9% of the reported new tumor cases and 71.8% of mortality cases, also ranking it first in tumor morbidity and mortality [1].

Lung cancer is now considered the most common malignant tumor in various countries and regions. In the classification of lung cancer,

non-small cell lung cancer (NSCLC) is the most common, which comprises 85% of all lung cancer cases [2]. In general, lung cancer is often diagnosed in the late and advanced stages, where the patients already present with metastasis [3, 4]. In most patients with advanced NSCLC, the therapeutic efficacy was reported to be poor even after chemotherapy, and the five-year survival rate was low. Studies have even shown that most patients progressed after first-line treatment with a therapeutic effectivity rate of 8%-10% even after second-line chemotherapy. The prognosis in patients with advanced NSCLC is generally poor as the median progression-free survival (PFS) was only about 2-4 months with a median overall survival (OS) of about 8-10 months [5].

Increasingly several studies have found that neovascularization played an important role in

the tumor development [6]. Inhibition of neo-vascularization has now become a great area of interest in scientific research. Blood vessels can disorder tissue structure and heterogeneity, which may promote tumor growth by providing oxygen and nutrients. Then tumor cells are allowed to escape into the blood circulation, which eventually leads to tumor metastasis [7, 8]. Therefore, vascular endothelial growth factor (VEGF), is an important factor in promoting angiogenesis and is becoming a new target in the treatment of tumors [9]. As a monoclonal antibody against VEGF, bevacizumab can inhibit the binding of VEGF to its receptor which inhibits tumor angiogenesis while promoting degeneration of tumor new vessels and normalization of survival vessels, ultimately inhibiting tumor growth and metastasis. Multiple studies have found that bevacizumab has an inhibitory effect on VEGF in tumor treatment. Particularly, it has a good therapeutic effect on NSNSCLC without increasing the incidence of adverse effects.

In a single-center study, the objective remission rate (ORR) of weekly paclitaxel combined with bevacizumab in the second- and third-line treatment of advanced NSNSCLC was 22.5%, and the median PFS was 5.4 months [10]. Kurishima et al. also found that the ORR and median PFS of docetaxel combined with bevacizumab in the second- and third-line treatment of NSCLC were 26.7% and 5.9 months, respectively [11]. Yamada et al. treated 28 NSNSCLC patients with retreatment of tegafur combined with bevacizumab [12], the median PFS was 3.2 months, and the median OS was 11.4 months, the ORR and disease control rate (DCR) were 14.3% and 85.5%, respectively.

However, some studies still doubt the efficacy of bevacizumab in combination with chemotherapy [13-16]. Thus, the objective of this study was to evaluate the efficacy of bevacizumab in combination with chemotherapy in the treatment of advanced NSNSCLC, providing further scientific evidence for the clinical application of bevacizumab.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of Gansu Provincial Cancer Hospital, Gansu Provincial Academic Institute for Medical Research. From March 2016 to December 2017, 72 patients with advanced NSNSCLC were admitted to the Gansu Provincial Cancer Hospital, Gansu Provincial Academic Institute for Medical Research and were included in this retrospective study. Based on whether or not bevacizumab was used with chemotherapy, they were divided into an observation group and control group, with 36 cases in each group. The observation group (36 cases) was divided into a combination group (n=23) and single drug group (n=13) according to whether bevacizumab was used in the maintenance therapy or not. The age of the patients ranged from 18 to 75 years old with an average age of 53.5±8.7 years. All patients included in this study signed a consent form.

Inclusion criteria: Patients diagnosed with advanced NSCLC, and patients diagnosed with NSNSCLC by fiberoptic bronchoscopy biopsy. It was diagnosed, based on the Tumor Node Metastasis staging of lung cancer established by the Union for International Cancer Control/American Joint Committee on Cancer in 2017, as stage III-IV [2]. Patients with tumor lesions that could be measured or evaluated by imaging. Patients with mean survival time of more than 3 months as expected. Patients with normal coagulation function and bone marrow function. Patients with normal cardiopulmonary function. Patients with imaging exclusion of central nervous system metastases and important vascular involvement. Patients with a physical fitness score of 0 to 2 according to the Eastern Cooperative Oncology Group [17]. Patients with complete clinical data.

Exclusion criteria: Patients who have received or are currently undergoing other chemotherapy. Patients with severe cardiopulmonary disease. Patients complicated with other primary malignant tumors. Patients with abnormal coagulation or bone marrow function. Patients with liver and kidney dysfunction. Patients allergic to chemotherapy drugs. Patients who cannot cooperate.

Methods

The observation group was treated with bevacizumab and pemetrexed plus platinum chemotherapy regimen. To be specific, intravenous infusion of 7.5 mg/kg bevacizumab (Shanghai

Roche Pharmaceutical Co., Ltd.) combined with 500 mg/m^2 pemetrexed (Jiangsu Haosen Pharmaceutical Co., Ltd.) on the first day, and combined with platinum chemotherapy. Patients received chemotherapy every three weeks, and two doses of chemotherapy as a course of treatment. The efficacy was evaluated after one course of treatment.

The maintenance treatment of the observation group began at 6 weeks after chemotherapy. The maintenance treatment regimen: For the combination group, the bevacizumab was combined with pemetrexed on the first day with the same dose and usage method as mentioned above. For the single drug group, 500 mg/m^2 pemetrexed alone was intravenously infused on the first day. Maintenance treatment was repeated once every three weeks in both groups.

The chemotherapy regimens used in the control group were as follows: intravenous infusion of 500 mg/m^2 pemetrexed, combined with platinum chemotherapy. Patients received chemotherapy every three weeks, and two doses of chemotherapy as a course of treatment. Maintenance treatment of the control group was the same as the single group. The efficacy of the treatment was evaluated after one course of treatment.

All patients were orally treated with multivitamin with minerals tablets which included folic acid (Beijing Xinhui Pharmaceutical Co., Ltd.) and vitamin B12 (Beijing Zizhu Pharmaceutical Co., Ltd.) at least 5 days before the initiation of treatment up until 21 days post-chemotherapy. Patients were administered with 1 mg vitamin B12 (Shanghai No.1 Biochemical & Pharmaceutical Co., Ltd.) intramuscularly before the first chemotherapy which was repeated every three cycles. Dexamethasone (Tianjin Lisheng Pharmaceutical Co., Ltd.) was given orally a day before, on the day, and a day after the use of pemetrexed, with a dosage of 4 mg/dose, twice a day as routine pretreatment in preventing allergies. Vitamin B12 and folic acid were given before chemotherapy to prevent anemia and other adverse effects on hematologic system. Blood transfusion was also available in severe cases. Leucocyte increasing agent was given once leukocytopenia was apparent. Nausea, vomiting, abdominal distention and diarrhea were addressed with therapy of acid suppres-

sion, stomach protection, antiemetic and regulation of intestinal flora. For the damage of liver function and kidney function and heart function, liver protection, kidney protection and improvement of heart function and other symptomatic treatment were given according to its severity. Bleeding was treated by platelet transfusion and hypertension by antihypertensive drugs.

Efficacy evaluation

Short-term efficacy: Evaluation of therapeutic efficacy was done after 12 weeks of treatment: measures of efficacy were divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) [18]. CR was defined as the resolution and disappearance of all lesions, the non-occurrence of new lesions, the maintenance of all tumor markers at levels below the upper limit, with this state maintained for at least 4 weeks. PR was referred as the sum of the maximum diameters of tumors decreasing by at least 30% which is maintained for more than 4 weeks. PD was defined as the sum of the maximum diameter of tumor target lesion increased by at least 20% in comparison to the minimum value during the observation period, or the discovery of new lesions. SD referred to the change of tumor between PR and PD, which indicated that the sum of the maximum diameter of the lesion was not reduced to the standard of PR, or the sum of the maximum diameter of the lesion did not increase to the standard of PD. ORR (%) = (CR + PR)/total number of cases. DCR (%) = (CR + PR + SD)/total number of cases.

Long-term efficacy: In the assessment of long-term efficacy, five-year PFS was used which was defined as the time at which the tumor progressed or metastasized to other parts of the body during treatment.

Toxic reactions

According to the National Cancer Institute - Common Toxicity Criteria 4.0 classification of toxic reactions, the adverse reactions of chemotherapeutic drugs included blood system toxicity and other systems such as nausea and vomiting, diarrhea, constipation, liver dysfunction, renal dysfunction, cardiac dysfunction, alopecia, and peripheral nervous system toxic-

ity. The above toxic effects were classified into 0-4 grades according to the different conditions which were measured as follows [19].

For hematological toxicity, the leukocyte toxic reaction was graded as grade 0: $\geq 4.0*10^9$/L; grade 1: $3.0-3.9*10^9$/L; grade 2: $2.0-2.9*10^9$/L; grade 3: $1.0-1.9*10^9$/L; grade 4: $<1.0*10^9$/L in terms of white blood cell levels.

The hemoglobin toxic reaction was graded as grade 0: ≥ 110 g/L; grade 1: 95-109 g/L; grade 2: 80-94 g/L; grade 3: 65-79 g/L; grade 4: <65 g/L in terms of hemoglobin levels.

Nausea and vomiting were graded as grade 0: none; grade 1: nausea; grade 2: temporary vomiting; grade 3: vomiting that needed treatment; grade 4: vomiting that was difficult to control.

Diarrhea was graded as grade 0: none; grade 1: transient diarrhea (≤ 2 days); grade 2: tolerable diarrhea (>2 days); grade 3: intolerable diarrhea that needed treatment; grade 4: bloody diarrhea.

Constipation was graded as grade 0: none, grade 1: mild constipation, grade 2: moderate constipation, grade 3: abdominal distension, grade 4: abdominal distension and vomiting.

Hepatic dysfunction was graded as grade 0: $\leq 1.25*N$; grade 1: $1.26-2.50*N$; grade 2: $2.6-5.0*N$; grade 3: $5.1-10.0*N$; grade 4: $>10*N$ in terms of bilirubin or alanine aminotransferase levels.

Renal dysfunction was graded as grade 0: $1.25*N$; grade 1: $1.26-2.50*N$; grade 2: $2.6-5.0*N$; grade 3: $5.1-10.0*N$; grade 4: $>10*N$ in terms of urea nitrogen or creatinine levels.

Cardiac dysfunction was graded as grade 0: normal; grade 1: asymptomatic, but with abnormal cardiac signs; grade 2: transient cardiac insufficiency, but no treatment needed; grade 3: symptomatic, cardiac insufficiency, treatment was effective; grade 4: symptomatic, cardiac insufficiency, treatment was ineffective.

Bleeding was graded as grade 0: none; grade 1: mild bleeding, not requiring any blood transfusion; grade 2: obvious bleeding, requiring infusion of 1-2 units of platelet concentrates; grade 3: obvious bleeding that required infusion of 3-4 units of platelet concentrates; grade 4: excessive bleeding requiring infusion of >4 units of platelet concentrates.

Hypertension was graded as grade 0: normal; grade 1: asymptomatic, diastolic blood pressure increased transiently >20 mmHg, previous normal blood pressure rose to 150/100 mmHg, no treatment was needed; grade 2: frequently or continuously present or symptomatic, the increase of diastolic blood pressure >20 mmHg or the past was normal with blood pressure >150/100 mmHg; grade 3: treatment was needed; grade 4: hypertensive crisis.

Statistical indicators

Using SPSS 17.0 statistical software, the continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm sd$). t-test was used in analyzing the data conforming to the normal distribution and homogeneity of variance, otherwise the rank sum test was used. The count data were expressed as cases/percentage (n/%) by using Pearson chi-square test or exact probability method. Survival analysis was done by utilizing the Kaplan-Meier method and Log-rank test. The difference is statistically significant when P<0.05.

Results

Comparison of general data

There were no significant differences in terms of gender, age, grade differentiation, cTNM stage, lymph node metastasis and physical fitness score between the observation group and control group (all P>0.05). See **Table 1**.

Comparison of efficacy

The ORR of the observation group was 36.11%, which was significantly higher than 13.89% of the control group (P<0.05). The DCR in the observation group was 86.11%, which was higher than 75.00% in the control group, although there was no statistical difference between the two groups (P>0.05). See **Table 2**.

Comparison of long-term efficacy

In terms of long-term efficacy, the PFS of the observation group was 17.7 months (95% CI: 15.60-19.89), which was significantly higher than the 11.6 months of the control group (95%

Table 1. Comparison of general information and data base

Item	Observation group (n=36)	Control group (n=36)	χ^2/t	P
Gender (male:female)	21:15	20:16	-0.236	0.813
Age	53.5±9.3	53.6±8.6	-0.040	0.969
Grade differentiation (n, %)			0.453	0.650
High	7 (19.44)	9 (25.00)		
Middle	16 (44.44)	15 (41.67)		
Low	13 (36.11)	12 (33.33)		
cTNM stage (n, %)			0.737	0.461
Stage III	25 (69.44)	22 (61.11)		
Stage IV	11 (30.56)	14 (38.89)		
Lymph node metastasis (n, %)				
Stage 0-1	7 (19.44)	6 (16.67)		
Stage 2-3	29 (80.56)	30 (83.33)		
Physical fitness score (n, %)			0.591	0.554
0-1 score	30 (83.33)	28 (77.78)		
2 scores	6 (16.67)	8 (22.22)		

Note: TNM, tumor node metastasis.

Table 2. Comparison of efficacy after 12 weeks of treatment (n, %)

Item	Observation group (n=36)	Control group (n=36)	χ^2	P
Measures of efficacy			4.550	0.031
CR	0 (0)	0 (0)		
PR	13 (36.11)	5 (13.89)		
SD	18 (50.00)	22 (61.11)		
PD	5 (13.89)	9 (25.00)		
Objective remission rate	13 (36.11)	5 (13.89)	2.203	0.043
Disease control rate	31 (86.11)	27 (75.00)	1.183	0.237

Note: CR, complete remission; PR, partial remission; SD, stable disease; PD, progression progressive disease.
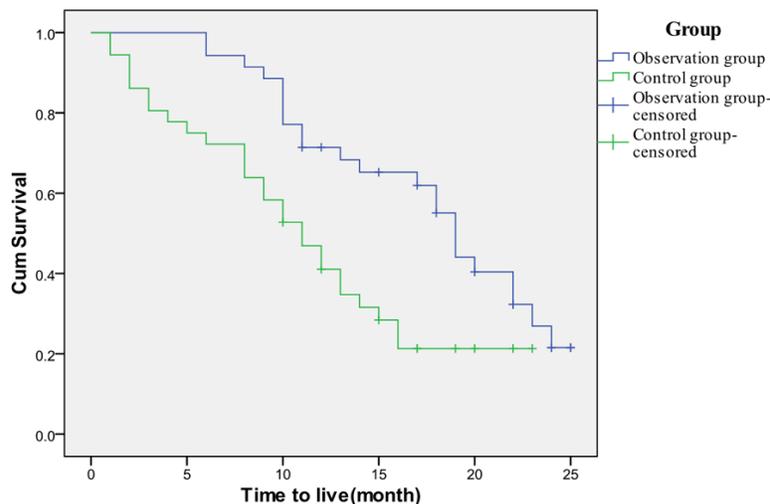

Figure 1. Comparison of long-term efficacy.

CI: 9.23-14.07; χ^2=7.783, P=0.005). See **Figure 1**.

Comparison of the efficacy of different maintenance regimens

After 6 weeks of treatment, 36 patients in the observation group were divided into combination group and single drug group based on various maintenance regimens, and the two groups were compared. Among them, 23 cases were treated with bevacizumab combined with pemetrexed at the same time, and 13 cases were treated with pemetrexed alone. As for short-term efficacy, no significant difference between the two groups in terms of ORR and DCR was found (P>0.05). The PFS of the combination group was 19.9 months (95% CI: 17.74-22.16), which was significantly higher than the 13.0 months of the single drug group (95% CI: 9.59-16.40; χ^2=7.626, P=0.006). See **Table 3** and **Figure 2**.

Comparison of adverse effects

In terms of adverse effects, there was a significantly higher incidence of hypertension in the observation group in comparison with the control group (P<0.05). While no statistical differences in other adverse effects were found between both groups (P>0.05). These adverse effects were tolerable after symptomatic treatment. See **Table 4**.

Discussion

Because of the low 5-year survival rate of the patients with lung cancer even after

Table 3. Comparison of the short-term efficacy of different mainte-
nance regimens in the treatment of patients (n, %)

Item	Combination group (n=23)	Single drug group (n=13)	χ^2	P
Measures of efficacy			0.471	0.673
CR	0 (0)	0 (0)		
PR	9 (39.13)	4 (30.77)		
SD	11 (47.83)	7 (53.85)		
PD	3 (13.04)	2 (15.38)		
Objective remission rate	9 (39.13)	4 (30.77)	0.495	0.697
Disease control rate	20 (86.96)	11 (84.62)	0.192	0.922

Note: CR, complete remission; PR, partial remission; SD, stable disease; PD, pro-
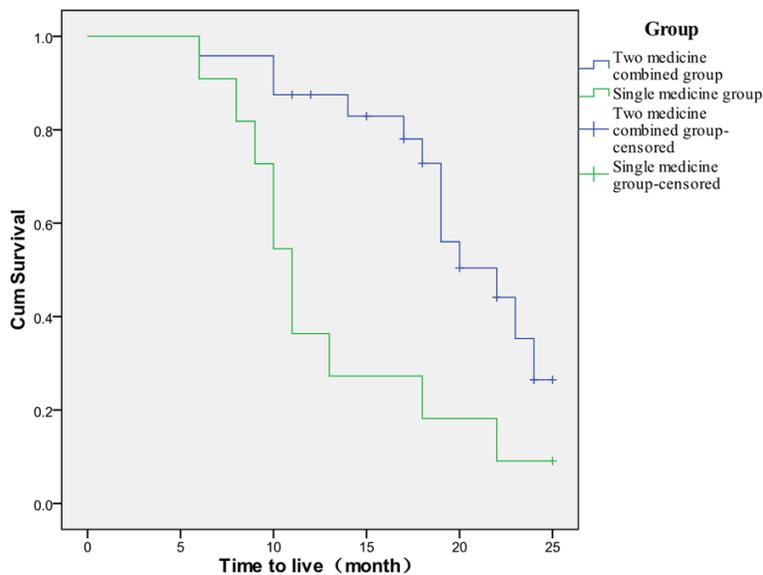gression progressive disease.

Figure 2. Comparison of the long-term efficacy of different maintenance regi-
mens.

respectively, and the ORR was 22.2% and 2.2%, respectively. The DCR was 62.2% in both groups. The random AVAPERL study evaluated the efficacy of maintenance therapy using bevacizumab plus pemetrexed and of using bevacizumab alone [22]. The dual drug maintenance has a significant benefit on PFS in patients with advanced NSCLC with no progression compared to using bevacizumab alone (10.2 months vs. 6.6 months).

In this present study, we found that the ORR of the observation group who received bevacizumab in combination with chemotherapy was significantly higher than that of the control group who only received single drug chemotherapy. The DCR was also higher than that of the control group, although there was no statistical difference between the two groups.

In terms of long-term efficacy, the PFS of the observation group was 17.7 months, which was higher than 11.6 months of the control group, and the difference was statistically significant. Further comparison was made among the patients in the observation group. The PFS was significantly higher in the group (19.9 months) who received a combination maintenance therapy of bevacizumab with chemotherapy in comparison to that of the control group (13.0 months). The result was consistent with the above results indicating that the application of combination therapy of bevacizumab with chemotherapy could improve the efficacy. As it's suggested, the synergistic effect of bevacizumab and chemotherapeutic agents might be due to the fact that bevacizumab could induce the normalization of tumor blood vessels which improves the high pressure state of the stroma of malignant tumors and promotes the effective distribution of che-

treatment, the use of bevacizumab to inhibit angiogenesis has attracted clinical attention in order to improve the survival rate. A study by Quan et al. showed that after 2 cycles, the response rate was 5% and the DCR was 50%, with a median OS of 29.6 months in the 40 patients with NSNSCLC who received chemotherapy containing bevacizumab [20]. In this study, the ORR of all patients was 12.2%, the DCR was 82.9%, and the median PFS and OS were 4.6 months and 11.9 months, respectively. Nishino et al. reported that 45 patients in each group were treated with second-line therapy of docetaxel plus bevacizumab, and tegafur plus bevacizumab, respectively [21]. The median PFS was 3.9 months and 3.5 months,

Table 4. Comparison of the adverse effects (n, %)

	Observation group (n=36)		Control group (n=36)		χ²	P
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4		
Decrease in leukocyte	4 (11.11)	2 (5.56)	5 (13.89)	4 (11.11)	0.811	0.417
Decrease in hemoglobin	7 (19.44)	2 (5.56)	8 (22.22)	2 (5.56)	0.278	0.781
Decrease in thrombocyte	6 (16.67)	2 (5.56)	6 (16.67)	5 (13.89)	0.657	0.511
Nausea and vomiting	10 (27.78)	2 (5.56)	13 (36.11)	2 (5.56)	0.755	0.450
Abnormal liver function	4 (11.11)	1 (2.78)	4 (11.11)	4 (11.11)	0.808	0.419
Proteinuria	2 (5.56)	0 (0)	2 (5.56)	1 (2.78)		1.000
Hypertension	8 (22.22)	1 (2.78)	2 (5.56)	0 (0)	2.256	0.024
Hemorrhage	4 (11.11)	0 (0)	1 (2.78)	0 (0)		0.357

motherapeutic drugs into the tumor tissues [23].

In the study on adverse effects of bevacizumab, a large phase IV clinical trial, SAIL (n=2,212), was conducted to evaluate the safety of bevacizumab combined with first-line standard chemotherapy regimen in Chinese patients. According to the results of the subgroup analysis of Chinese patients, the incidence of adverse events with grade 3 or higher was lower (<9%) [24]. In this current study, the common chemotherapeutic responses of the two groups during the course of treatment included symptoms caused by dysfunction of the hematologic system and digestive system. There was no significant difference between the two groups in terms of the occurrence of leukopenia, hemoglobin reduction, thrombocytopenia, nausea and vomiting, liver dysfunction, proteinuria and hemorrhage. However, the incidence of hypertension of the observation group was significantly higher than that of the control group. Previous studies have reported that the most common side effects of bevacizumab were hypertension, and some studies have suggested that the occurrence of hypertension was positively correlated with the efficacy of using bevacizumab [25-27]. However, a number of studies suggested that the early elevation of blood pressure could not predict the efficacy of bevacizumab [28]. The incidence of hypertension in this study was consistent with the available scientific literature. Due to the small number of cases of hypertension in this study, no further study was conducted on the correlation with efficacy. Most of the adverse effects could be tolerated by patients after active symptomatic treatment allowing them to complete the course of their chemotherapeutic regimen,

which was also consistent with several studies reporting good tolerance of bevacizumab in combination with chemotherapy especially in elderly patients [29].

However, this present study has limitations including a small sample size which needs to be further expanded for research. In addition, as this study is a retrospective study but not prospective study, the further multicenter prospective study should be performed to observe the therapeutic effect of bevacizumab in combination with chemotherapy.

In conclusion, bevacizumab has been proven effective and safe in the treatment of patients with advanced NSNSCLC, which can be considered as a notable drug for clinical application and research.

Disclosure of conflict of interest

None.

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