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ORIGINAL ARTICLE

Clinical efficacy of bevacizumab combined with gemcitabine and cisplatin combination chemotherapy in the treatment of advanced non-small cell lung cancer

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Summary

Purpose: *To investigate the clinical efficacy of bevacizumab combined with gemcitabine and cisplatin (GP) combination chemotherapy in the treatment of advanced non-small cell lung cancer (NSCLC).*

Methods: *A total of 186 patients with advanced NSCLC who were admitted to the First Affiliated Hospital of Kunming Medical University from October 2013 to June 2016 were randomly divided into control group and observation group, with 93 cases in each group. Patients in the control group were treated with GP chemotherapy, while patients in observation group were treated with intravenous infusion of bevacizumab combined with GP chemotherapy. Treatment was administered for 3 courses, every 3 weeks. After treatment, clinical efficacy, tumor markers levels (CEA and CYFRA21-1), serum vascular endothelial growth factor (VEGF) levels and adverse reactions were compared between two groups.*

Results: *After treatment, the total effective rate and disease control rate in the control group were 40.86% and 70.97%, respectively, while the total effective rate and disease control rate in the observation group were 70.97% and 90.32% respectively, ($p<0.05$). After treatment, the levels of CEA, CYFRA21-1 and serum VEGF in both groups were significantly lower than those before treatment ($p<0.05$), and decreases were more significant in the observation group than in the control group ($p<0.05$). The overall 1-, 3- and 5-year survival rates were 52.69% (49 cases), 36.56% (34 cases) and 25.81% (24 cases) for the observation group, and 43.01% (40 cases), 27.96% (26 cases) and 15.05 % (14 cases) for the control group. Overall survival rate in the observation group was significantly higher than the one in the control group ($p<0.05$).*

Conclusion: *The combination of bevacizumab plus GP chemotherapy for advanced NSCLC can improve serum tumor markers and clinical efficacy, thus prolonging the long-term survival of patients. It is worthy of clinical application.*

Key words: *advanced non-small cell lung cancer, bevacizumab, survival rate, clinical effect, GP chemotherapy*

Introduction

Lung cancer is one of the major types of malignancies with unacceptable high morbidity and mortality. There are two main types of lung cancer, small cell lung cancer (SCLC) and NSCLC, among

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which NSCLC is more common. Lung cancer at early stage usually shows no obvious symptoms, and most patients were diagnosed at advanced stages. Patients with advanced NSCLC were usually treated with radiotherapy and chemotherapy combined treatment [1-3]. In recent years, chemotherapy has become a standard treatment for NSCLC. The combination of platinum analogs and third-generation chemotherapy drugs has become the first-line standard treatment for patients with advanced NSCLC [4]. Clinical studies have shown that 2-year survival of NSCLC treated with gemcitabine combined with cisplatin (GP regimen) is relatively good. However, chemotherapeutic drugs can cause side effects, which limit their application to a great extent [5-7]. Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody that exerts a biological effect mainly by neutralizing VEGF and blocking its binding to the corresponding receptor on endothelial cells. At present, quite a few clinical studies have confirmed bevacizumab-combined chemotherapy can significantly prolong the median survival of patients [8-10].

This study observed and analyzed the clinical efficacy of bevacizumab combined with GP chemotherapy in the treatment of advanced NSCLC with the expectation of providing guidance for the treatment of advanced NSCLC.

Methods

General information

A total of 186 patients with advanced NSCLC who were admitted to the First Affiliated Hospital of Kunming Medical University from October 2013 to June 2016 were enrolled. All patients were treated for the first time and all of them were pathologically diagnosed with NSCLC. Patients were divided into IIIB and IV stages according to TNM staging system, and the estimated survival was about 3 months.

Exclusion criteria: (1) patients received surgery or got trauma within a month before admission; (2) patients with visible hemoptysis; (3) patients with CNS metastasis; (4) patients with uncontrollable hypertension; (5) patients with severe mental disorder.

The patients were randomly divided into the control group and observation group with 93 cases in each group. The control group included 52 males and 41 females, aged between 42 to 75 years (mean 58.3 ± 10.6). The observation group included 55 males and 38 females, aged from 40 to 75 years (mean 57.9±11.2). No significant differences in general information were found between two groups ($p>0.05$). The study was approved by the ethics committee of the First Affiliated Hospital of Kunming Medical University and informed consents were signed by the patients and/or their guardians.

Treatment methods

Patients in control group received GP chemotherapy: intravenously administration of gemcitabine (1000 mg/m^2) was performed on day 1 and 8, and intravenously administration of cisplatin (75 mg/m^2) was performed on day 1 and 3. Besides GP chemotherapy, bevacizumab treatment was also performed in observation group: intravenously administration of bevacizumab (7.5 mg/kg) was performed on day 1. Treatment was performed for 3 courses, and 21d for each course.

Detection of serum tumor markers (CEA and CYFRA21-1) levels before and after treatment

Fasting peripheral venous blood (3 ml) was taken from each participant in the morning. Blood was kept at room temperature for 2 hrs, followed by centrifugation at 3000 rpm/min for 10 min to collect serum. Serum was stored at -20°C. Detection of serum CEA and CYFRA21-1 was performed by electrochemiluminescence immunoassay.

Serum VEGF levels before and after treatment testing

Serum VEGF levels were measured by double antibody sandwich enzyme-linked immunosorbent assay (ELISA) in strict accordance with the instructions of the ELISA kit. All experiments were performed 3 times using double-blind method, and the average value was calculated. Optical density (OD) value was measured at 450 nm, and VEGF content was calculated according to the standard curve.

Short-term outcomes

RECIST solid tumor evaluation was performed 1 month after treatment. Complete remission (CR): original lesions disappeared with disappearance duration >4 weeks; Partial remission (PR): reduction of target lesion ≥30%, for ≥4 weeks; stable (SD): didn't meet PR criteria but the lesion did not increase; Progression (PD): The target lesions were enlarged or new lesions appeared. Total efficiency (%)=(CR+PR)/total number of cases×100%; disease control rate (%)=(CR+PR+SD)/total number of cases×100%.

Table 1. Comparison of serum tumor marker levels between two groups before and after treatment

Groups	*Cases (n)*	*CEA (ng/Ml)*		*CYFRA21-1 (ng/Ml)*	
		Before treatment	*After treatment*	*Before treatment*	*After treatment*
Observation	93	61.03±7.32	18.27±4.11*#	49.13±5.82	13.45±3.68*#
Control	93	58.78±7.19	29.56±5.23*	51.61±5.43	25.33±4.05*

*compared with pretreatment level within the same group; #compared with control group after treatment

Long-term outcomes

After treatment, patients in both groups were followed up for more than 36 months. The 1, 2 and 3-year cumulative survival rates of the two groups were analyzed by Kaplan-Meier survival analysis with log-rank test.

Statistics

SPSS17.0 statistical software was used. Comparisons of continuous data between two groups were performed using Student's *t*-test. Categorical data were analyzed by chi-square test. Log-rank was used to compare the cumulative survival rate and cumulative recurrence rate. P<0.05 was considered to be statistically significant.

Results

Serum tumor markers (CEA, CYFRA21-1) levels before and after treatment

As shown in Table 1, the levels of CEA and CYFRA21-1 after treatment in both groups were significantly lower than those before treatment (p<0.05), and decreases were more significant in the observation group than in the control group (p<0.05).

Comparison of serum VEGF levels between the two groups before and after treatment

As shown in Table 2, compared with pretreatment levels, serum VEGF levels dropped significantly in the observation group (p<0.05), while no significant changes in serum VEGF levels were found in the control group after treatment (p>0.05).

Table 2. Comparison of serum VEGF levels between two groups before and after treatment

Groups	*Cases (n)*	*VEGF (ng/Ml)*	
		Before treatment	*After treatment*
Observation	93	189.25±67.36	109.27±52.17*#
Control	93	193.78±70.13	181.52±60.37

*compared with pretreatment level within the same group; #compared with control group after treatment

Comparison of short-term outcomes between the two groups

Comparisons of short-term outcomes between two groups within 1 month after treatment are shown in Table 3. In the control group, 9 cases of CR, 29 cases of PR, 28 cases of SD and 27 cases of PD were observed, and the total effective rate and disease control rate were 40.86% and 70.97%, respectively. In the observation group, 23 cases of CR, 43 cases of PR, 18 cases of SD and 9 cases of PD were observed, and the total effective rate and disease control rate were 78.49% and 90.32%, respectively (p<0.001).

Comparison of long-term outcomes between the two groups

The 2 groups of patients were followed up for 36 months after treatment. There were 69 deaths in the observation group and 79 deaths in the control group (p<0.05). Kaplan-Meier survival curve showed that 1-, 3- and 5-year overall survival rates were 52.69% (49 cases), 36.56% (34 cases) and 25.81% (24 cases) for the observation group, and 43.01% (40 cases), 27.96% (26 cases) and 15.05 % (14 cases) for the control group. Log-rank test showed that overall survival rate in the observation group was significantly higher than the one in control group (p<0.05).

Discussion

Surgical resection is the most effective treatment for early stage NSCLC, but the majority of patients with NSCLC are diagnosed at advanced stages, which are not appropriate for surgical operations. Median survival of NSCLC patients in advance stages is only 8-10 months, and a significant proportion of those who undergo complete resection eventually die of tumor recurrence and metastasis [11,12]. Treatment of patients with advanced NSCLC is mainly radiotherapy and chemotherapy, combined or not. Platinum analogs combined with third-generation chemotherapy drugs have become the first-line treatment for advanced NSCLC patients. Extensive *in vitro* and *in vivo* test results confirm that gemcitabine has synergistic effects

Table 3. Comparison of efficacy in the control group and observation group

Groups	*Cases (n)*	*CR n (%)*	*PR n (%)*	*SD n (%)*	*PD n (%)*	*Total effective rate (%)*	*Disease control rate (%)*
Observation	93	4 (4.30)	35 (37.63)	45 (48.39)	9 (9.68)	41.94*	90.32*
Control	93	1 (1.08)	27 (29.03)	45 (48.39)	20 (21.51)	30.11	78.49

*compared with control group, p<0.05

with cisplatin in inhibiting the repair of DNA that is damaged by cisplatin. However, chemotherapeutic drugs not only kill the tumor cells but also kill normal cells and cause many adverse reactions. Therefore, development of targeted drugs with low toxicity and high efficiency has become the focus of current clinical research [13,14].

Studies have shown that tumor growth and metastasis are closely related to the density of tumor blood vessels. Blood vessels not only provide abundant nutrition for the growth of the tumor, but also exclude metabolites of the tumor cells and facilitate tumor metastasis. Therefore, in clinical anti-tumor research, anti-angiogenesis has become one of the main targets of tumor treatment [15]. VEGF is a key regulator of angiogenesis and stimulates the proliferation of endothelial cells and the formation of blood vessels *in vivo*. Studies have shown that VEGF expression level increased significantly in tumor-bearing models established using lung cancer cell lines and human lung cancer tissue. VEGF signaling pathway plays an important role in maintaining the growth, proliferation and migration of tumor cells [15-17]. Therefore, VEGF and its receptor VEGFR have become important targets for anti-tumor therapy. Both *in vitro* and *in vivo* studies have demonstrated that bevacizumab can bind to human VEGF to block its biological function and exert an anti-angiogenic effect [18]. In this study, bevacizumab combined with GP chemotherapy was used to treat advanced NSCLC and the clinical efficacy of the combination was explored. Results showed that compared with chemotherapy alone, the combined treatment significantly improved serum markers CEA and CYFRA21-1. Further measurement of serum VEGF levels in patients showed that these levels decreased significantly in patients treated with combination therapy, while serum VEGF levels in patients with chemotherapy alone did not change significantly, indicating that bevacizumab exerted its effect of inhibiting angiogenesis. Evaluation of treatment outcomes showed that total effective rate and disease control rate of patients treated with combined therapy were significantly higher than those of patients treated with chemotherapy alone. The 36-month follow-up results showed that the 3-year cumulative survival rate of the combination therapy group was significantly higher than that of the simple therapy group.

In summary, bevacizumab combined with GP chemotherapy in the treatment of advanced NSCLC can significantly improve the level of serum tumor markers and effectively improve the clinical efficacy, thereby prolonging the survival of patients and we believe that this treatment should be popularized in clinical practice.

Authors' contributions

JD was responsible for the conception and design of this study. ZY was mainly devoted to the collection and assembly of data. DL was responsible for data analysis and interpretation. ZZ was a contributor in manuscript writing. YS performed the research and finalized this paper. All authors read and approved the final manuscript.

Conflict of interests

The authors declare no conflict of interests.

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