RESEARCH ARTICLE

Clinical Efficacy of Bevacizumab Concomitant with Pemetrexed in Patients with Advanced Non-small Cell Lung Cancer

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Abstract

Objective: To observe the clinical efficacy of bevacizumab concomitant with pemetrexed in patients with advanced non-small cell lung cancer (NSCLC). Materials and Methods: A total of 72 patients were randomly divided into a combination group (pemetrexed+bevacizumab, n=36) and a pemetrexed group (n=36) and assessed for disease control (CR+PR+SD) after 4-cycles of first-line GP chemotherapy (gemcitabine+cisplatin). Clinical efficacy, progression-free survival time (PFS), overall survival time (OS), overall response rate (ORR), disease control rate (DCR) and rate of adverse responses between two groups were observed and compared. Results: ORR and DCR were 27.8% and 83.4% in combination group, and 16.7% and 69.5% in the pemetrexed group, respectively, but there were no significant differences (*P*>0.05). PFS in combination group and pemetrexed group were 4.6 months and 3.9 months respectively (*P*=0.09), whereas OS in the combination group was 14 months, evidently higher than in the pemetrexed group (11 months, *P*=0.004). Adverse responses in both groups included high blood pressure, bleeding, thrombocytopenia, anemia, elevated transaminase, diarrhea, vomiting and proteinuria, but there were no significant differences (*P*>0.05). Conclusions: Bevacizumab concomitant with pemetrexed has better clinical efficacy and safety, giving rise to prolonged survival time in patients with advanced NSCLC.

Keywords: Bevacizumab - pemetrexed - combined treatment - non-small cell lung cancer

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Introduction

Bevacizumab is a recombinant humanized monoclonal antibody used for multiple solid tumors in recent years, including lung cancer (Gentzler et al., 2013; Smith et al., 2013). At present, maintenance chemotherapy is a new perspective for advanced non-small cell lung cancer (NSCLC), which refers to the maintenance therapy in a certain period of induction chemotherapy to achieve the maximum tumor response, according to the additional chemotherapy which can prolong the survival time of patients by extending the total schedule of chemotherapy to achieve its higher total dose (Brattstorm et al., 2004; Akkuzu, 2012; Chen et al., 2012; Liu et al., 2012; Karayama et al., 2013; Alimujiang et al., 2013; Tai et al., 2013; Ugur et al., 2014). Therefore, this study aimed to explore whether bevacizumab concomitant with pemetrexed could provide benefits for patients with advanced cancers by observing their influence on the clinical efficacy, safety and survival time after first-line treatment of platinum-based chemotherapy in advanced NSCLC patients admitted in our hospital from May 2009 to May 2011.

Materials and Methods

Materials

Of the 72 advanced NSCLC patients with adenocarcinoma diagnosed by pathology or cytology, there were 48 males and 24 females, aging 38~73 years, with median age being 65 years. TNM stage: 43 patients in phase III B and 29 in phase IV. According to Eastern Cooperative Oncology Group (ECOG) scores, 14 patients were with 0 score, 32 with 1 score, 17 with 2 scores and 9 with 3 scores. Additionally, of all patients, 44 were with smoking history and 28 without. All patients were randomly divided into combination group and pemetrexed group, 36 cases for each. Tumor lesions, hepatorenal functions and blood tests were measurable and in normal values in both groups. Meanwhile, from January on, no other anti-cancer therapy was applied. The general data of two groups was shown in Table 1, and the differences were not statistically significant (*P*>0.05).

Methods

All patients were treated with GP protocol: Gemcitabine 1 000 mg/m^2, on d1 and d8; cisplatin 75 mg/m^2, on d1, 21

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Table 1. Comparison of General Data Between Two Groups

		Combination group	Pemetrexed group	Total
Age/years	<65	12	10	22
	≥65	24	26	50
Gender	Male	25	23	48
	Female	11	13	24
ECOG score	0	5	9	14
	1	18	14	32
	2	10	7	17
	3	3	6	9
TNM stages	Phase IIIB	22	21	43
	Phase IV	14	15	29
Smoking history	No	13	15	28
	Yes	23	21	44

d as a cycle. After 4 cycles , the disease control rate (DCR) (CR+PR+SD) of both groups were evaluated. Then, pemetrexed group was intravenously administrated with 500 mg/m^2 pemetrexed on d1, 3 weeks as a cycle, and the indexes were evaluated after 2 cycles. Before pemetrexed treatment, 400 μg/d folic acid was orally given until the end; intramuscular injection of 1000 μg vitamin B12 was performed, once every 9 weeks; 4 mg/time dexamethasone tablet was orally administrated during d1~2, 2 times/d. The above therapies were repeated every 3 weeks until disease progression. On the basis of above therapy, the combination group was added with intravenous injection of 5 mg/kg (on body weight) bevacizumab, once every 2 weeks.

Observational indexes

After 2-cycle treatment following 4-cycle GP chemotherapy, clinical efficacy, progression-free survival time (PFS), overall survival time (OS), overall response rate (ORR), disease control rate (DCR) and rates of adverse responses between two groups were evaluated and compared.

Evaluation Criteria

Clinical efficacy: Clinical efficacy was divided into complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), according to WHO Response Evaluation Criteria In Solid Tumors. Clinical ORR= (CR+PR)/total cases×100%. DCR= (CR+PR+SD)/ total cases×100%.

Survival time: After 4-cycle GP chemotherapy, PFS and OS were evaluated after the first cycle of chemotherapies. PFS was defined as the duration from the beginning of treatment to tumor progression on any part of body, while OS from the beginning of treatment to the deaths (by any reasons) of advanced NSCLC patients.

Adverse responses: The adverse responses were divided into degree 0, I, II, III and IV according to WHO Grade Scale for Acute and Sub-acute Toxicity of Anti-cancer Drugs.

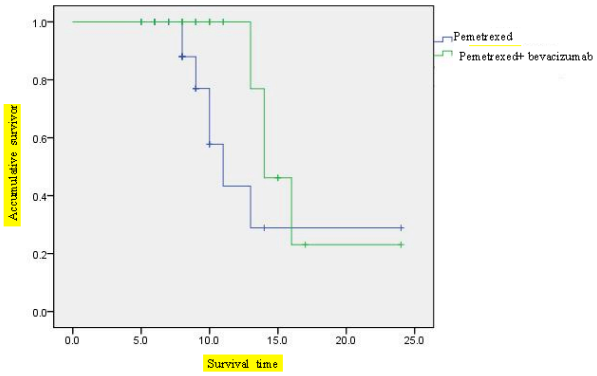

Figure 1. Comparison of PFS and OS between Two Groups

Statistical data analysis

SPSS17.0 software was used for all data analysis. X^2 was applied for the comparison of enumeration data between groups while T-test for measurement data. PFS and OS between two groups were analyzed by Kaplan-Meier method and Log-Rank test. $P<0.05$ was considered statistically significant.

Results

Clinical efficacy

After treatment, there was no CR in both groups, while PR, SD and PD were 10 (27.8%), 20 (55.6%) and 6 (16.7%) in combination group, and were 6 (16.7%), 19 (44.4%) and 11 (30.6%) in pemetrexed group, respectively. Additionally, the ORR and DCR were 27.8% and 83.4% in combination group, and were 16.7% and 69.5% in pemetrexed group, respectively, but there were no significant differences ($P>0.05$) (Table 2).

Adverse responses

Adverse responses in both groups included high blood pressure, bleeding, thrombocytopenia, anemia, elevated transaminase, diarrhea, vomiting and proteinuria, etc., but there were no significant differences ($P>0.05$). After 1- or 2-week rest, all patients were recovered from these adverse responses after symptomatic treatment (Table 3).

PFS and OS

The PFS in combination group was 4.6 months, higher than in pemetrexed group (3.9 months), but the difference was not significant ($\chi^2=3.272$, $P>0.09$). However, the OS in combination group was 14 months (95% CI: 12.5~15.5 months), obviously longer than the 11 months in pemetrexed group (95% CI: 8.8~13.1 months), and the difference were statistically significant ($\chi^2=6.372$, $P=0.012$), according to the Log-Rank test (Figure 1).

Table 2. Comparison of ORR and DCR Between Two Groups [n (%)]

Groups	n	CR	PR	SD	PD	ORR	DCR
Combination group	36	0 (0.0)	10 (27.8)	20 (55.6)	6 (16.7)	10 (27.8)	30 (83.4)
Pemetrexed group	36	0 (0.0)	6 (16.7)	19 (44.4)	11 (30.6)	6 (16.7)	25 (69.5)

Table 3. Comparison of Adverse Responses Between Two Groups (n)

Programs Degree	Combination group	Pemetrexed group	Total	*P*
Leukopenia				
0	24	23	47	0.804
I~II	12	13	25	
Thrombocytopenia				
0	32	33	65	1.000
I~II	4	3	7	
Fatigue				
0	21	24	35	0.465
I~II	15	12	27	
Anemia				
0	32	33	65	1.000
I~II	4	3	7	
Elevated transaminase				
0	31	30	61	0.743
I~II	5	6	11	
Bilirubin Elevated				
0	32	31	63	1.000
I~II	4	5	9	
Rash				
I~II	6	5	11	1.000
III~IV	2	3	5	
Mucositis				
0	33	33	66	1.000
I~II	3	3	6	
Vomiting				
0	29	30	59	0.759
I~II	7	6	13	
Diarrhea				
0	34	32	66	0.674
I~II	2	4	6	
Peripheral neuritis				
0	31	29	60	0.527
I~II	5	7	12	
Pulmonary hemorrhage/hemoptysis				
0	24	30	54	0.102
I~II	12	6	18	
Gastrointestinal Perforation				
0	29	30	59	0.759
I~II	7	6	13	
Bleeding				
0	30	32	62	0.496
I~II	6	4	10	
Arterial thromboembolism				
0	31	34	65	0.426
I~II	5	2	7	
Hypertension				
0	25	33	58	1.000
I~II	11	3	14	

Discussion

Pemetrexed is a multi-target synthetic anti-folate drug, the mechanism of which is to effectively inhibit the activities of thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonicleotide formyltransferase (GARFT) and to reduce the normal folate-dependent metabolism so as to inhibit the synthesis of purine and pyrimidine from multiple channels, thus preventing cell replication in phase S to achieve the anti-tumor effects. In recent years, studies showed that pemetrexed could be used and had certain effects on a variety of commonly seen tumors like lung cancer, colorectal cancer, breast cancer and pancreatic cancer, etc.. (Gerber et al., 2013; Zhang et al., 2013; Deng et al., 2013; Davis et al., 2012). National Comprehensive Cancer Network (NCCN) guidelines (2009) recommended that after first-line treatment of platinum-containing regimen or monotherapy, NSCLC patients with SD were considered to be effective after 4~6 cycles of pemetrexed chemotherapy, who could continue the original chemotherapy or added with maintenance therapy until disease progression. Ciuleanu reported a phase III clinical study, in which 663 NSCLC patients in phase IIIB or IV underwent 4 cycles of platinum-based chemotherapy were randomly divided into placebo combined with best supportive care group and pemetrexed combined with best supportive care group by ratio of 2 : 1, whose results showed that PFS (4.0 months vs. 2.0 months; HR: 0.60; $P<0.001$) and OS (13.4 months vs. 10.6 months; HR: 0.79; $P=0.012$) were significantly different between two groups and pemetrexed was more effective in prolonging the PFS and OS of patients (Ciuleanu, et al., 2009).

Bevacizumab, including 93% of human IgG fragments and 7% mice-originated structures, is a recombinant humanized monoclonal antibody that can selectively combine with vascular endothelial growth factor (VEGF) receptor against VEGF, which has higher affinity and anti-angiogenesis effect, becoming effective in preventing the interaction of VEGF and vascular endothelial cell surface receptor and inhibiting the endothelial cell proliferation and angiogenesis, then carrying out its anti-tumor effect (Chien et al., 2012; Sandomenico et al., 2012; Huang et al., 2014; Wu et al., 2014). One study reported 1 case of lung cancer in phase IIIA treated with bevacizumab in combination with paclitaxel and carboplatin, and the results were satisfactory (Kawaharada et al., 2012). It is more advisable for bevacizumab to be used together with other anti-tumor drugs in clinic other than being singly applied, therefore, based on medical ethics, bevacizumab was not singly utilized as any group in present studies. Several large clinical trials on NSCLC patients with platinum-based first-line chemotherapy indicated that the continuous application of bevacizumab as maintenance therapy could effectively prolong the survival time of patients (Lopez-Chavez et al., 2012; Stevenson et al., 2012; Stevenson et al., 2012; Kentepozidis et al., 2013). However, whether the application of bevacizumab as maintenance therapy can increase the rates of adverse responses is still inconclusive. In a large clinical study, patients with advanced non-squamous carcinoma in phase IV were performed with 6-cycle first-line treatment of bevacizumab combined with different chemotherapies, and then with bevacizumab as its maintenance therapy until disease progression, whose results suggested that continuous utilization of single bevacizumab would not evidently increase the rates of adverse responses in patients (Tsai, et al., 2011).

In this study, the clinical ORR and DCR in combination group were higher than in pemetrexed group, but the differences were not statistically significant, which needed more researches and study objects for further evaluation. However, this study also demonstrated that

bevacizumab was beneficial in controlling tumor growth when combined with pemetrexed, which had synergistic action with each other.

The adverse responses were tolerable in two groups in that no patients had discontinuous chemotherapy and the ECOG scores also showed favorable tolerability and better security. Neutropenia and fatigue in degree I/II were commonly occurred, while hematologic and non- hematologic toxicity in degree III/IV were rare. In addition, low-rate adverse responses between two groups showed no significant differences, indicating that bevacizumab concomitant with pemetrexed were available.

In this study, there were no significant differences between two groups in PFS, clinical ORR and DCR, but the difference in OS was statistically significant, indicating that bevacizumab concomitant with pemetrexed could markedly improve the clinical efficacy and the prognosis of patients with advanced NSCLC.

In summary, bevacizumab concomitant with pemetrexed is excellent in promoting the clinical efficacy and safety with tolerable adverse responses, which can also prolong the OS of patients with advanced NSCLC.

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