RESEARCH ARTICLE

Bevacizumab Concomitant with Chemotherapy is Effective in Treating Chinese Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer

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Abstract

Objectives: To retrospectively review the safety and clinical efficacy of bevacizumab concomitant with chemotherapy in Chinese patients with advanced non-squamous non-small cell lung cancer (NSNSCLC). Methods: Clinical data for 79 patients with NSNSCLC who received bevacizumab concomitant with chemotherapy in Chinese PLA General Hospital from April 28th 2009 to May 5th 2013 were retrospectively reviewed to analyze the clinical efficacy including disease control rate (DCR), overall response rate (ORR), progression-free survival (PFS), overall survival (OS), the Eastern Cooperative Oncology Group (ECOG) score and the safety. Results: The Eastern Cooperative Oncology Group (ECOG) score was 0-2. By the final cutoff date (June 9, 2013), 54 (68.4%) patients had disease progression and 37 (46.8%) died. The ORR was 32.9% and the DCR was 83.5%. The ORR of the first-, second-, and third- or later-line treatments were 51.4%, 25.0% and 12.5%, while the DCR were 94.3%, 80.0% and 70.8%, respectively. The median OS (mOS) and PFS (mPFS) were 13.5 and 5.83 months, respectively. The mOS of patients with the first-, second-, and third- or later- line treatments were 16.2, 10.9and 8.30 months, while the mPFS were 7.27, 5.90 and 5.17 months, respectively. Chemotherapy-related adverse events included myelosuppression, vomiting, hepatic dysfunction and renal dysfunction, while the common serious bevacizumab-related adverse events were thromboembolic problems, gastrointestinal perforation and reversible posterior leukoencephalopathy syndrome, which could be well managed. Conclusions: Bevacizumab concomitant with chemotherapy is effective and the related toxicity can be well tolerated in Chinese patients with NSNSCLC.

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

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Introduction

Lung cancer is the most common malignant cancer and the leading cause of cancer-related death in Asian Pacific Area (Mollazade et al., 2013; Takiar et al., 2013; Kang et al., 2013; Ma et al., 2013; Zhang et al., 2013; Huang et al., 2013; Wang et al., 2013; Piao et al., 2013; Liu et al., 2013; Xu et al., 2013; Mohammad et al., 2013). Over the years, lung cancer incidence and mortality have been increasingly improved steadily. It was recently estimated that 522, 050 cases of lung cancer were diagnosed and over 452 000 males and females died (Soerjomataram et al., 2012). Approximately 85% of all lung cancer cases are categorized as non-small cell lung cancer (NSCLC), and most patients present with advanced disease at the time of diagnosis (Juergens et al., 2007; Emal et al., 2009). The standard care for patients with advanced disease is double agent platinum-based chemotherapy (Stinchcombe et al., 2009). The Eastern Cooperative Oncology Group (ECOG) conducted a randomized clinical trial comparing 4 platinum-based two-drug chemotherapy regimens in more than 1 100 patients (Schiller et al., 2002), which reported that the median survival time (mOS) was 8 months, with no significant difference in overall survival (OS) among the groups. Therefore, it appears that the effect of the traditional platinum-based doublet chemotherapy reached a plateau, and that additional therapeutic options are needed. In addition, antibodies against vascular endothelial growth factor (VEGF, such as bevacizumab) have been shown to benefit patients with a variety of cancers (Cohen et al., 2009; Wu et al., 2009; Summers et al., 2010).

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that can selectively bind to and neutralize the biological activity of humanVEGF (Kerbel et al., 2002; Ferrara et al., 2004). In combination with several platinum-based double chemotherapy regimens, such as vinorelbine/cisplatin, gemcitabine/cisplatin, paclitaxel/cisplatin, and docetaxel/cisplatin, bevacizumab is approved by Food and Drug Administration (FDA) as the first-line treatment for advanced/metastatic non-small cell lung cancer (NSCLC) (Wu et al., 2009).

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Many studies have shown that bevacizumab and cytotoxic chemotherapy benefits patients with non-squamous NSCLC (NSNSCLC) (Johnson et al., 2004; Sandler et al., 2006; Eisenhauer et al., 2009; Niho et al., 2012; Kitamura et al., 2013). However, the vast majority of subjects participating in those studies were Caucasian patients, and the safety and efficacy of bevacizumab concomitant with chemotherapy regimens have not been clarified in Chinese patients with NSNSCLC. To fill this gap in knowledge, we proposed, in this retrospective review, to investigate the safety and efficacy of bevacizumab concomitant with chemotherapy on Chinese patients with NSNSCLC.

Materials and Methods

Materials

The clinical data of 79 patients with NSNSCLC who were given bevacizumab concomitant with chemotherapy from April 28th 2009 to May 5th 2013 in the Chinese PLA General Hospital were retrospectively reviewed. Of the 79 patients, there were 51 males and 28 females, aging 25-76 years, with median age being 56 years. The inclusion criteria: treatment with bevacizumab ≥2 times; with bi-dimensionally measurable disease; cytologically or histologically confirmed with NSNSCLC with one or more measurable lesion ≥10 mm in its longest diameter by spiral computed tomography (CT), or ≥20 mm with conventional techniques, according to Response Evaluation Criteria In Solid Tumors (RECIST version 1.0); age ≥20 years; life expectancy ≥12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2; adequate hematologic (an absolute neutrophil count >1 500/μL, hemoglobin >9.0 g/dL and platelet count >75 000/μL), hepatic (bilirubin <2.0 mg/dL and transaminase levels <3 times of the upper normal limit) and renal (creatinine <1.5 mg/dL and urinary excretion ≤500 mg of protein per day) functions. The exclusion criteria included the presence of clinically significant cardiovascular disease; uncontrolled hypertension history; unstable brain; any evidence of uncontrolled systemic diseases; non-healing wounds; major surgery within the preceding 6 weeks; the need for full-dose anticoagulation; preexisting coagulopathies or bleeding diatheses; pregnancy or lactation; and incomplete clinical data. After included, no other anti-cancer therapy was applied. All patients provided informed consents, and the experimental protocol was approved by the ethical committee of Chinese PLA General Hospital.

Methods

Of the 79 patients, 49 received bevacizumab combined with platinum-based two-drug chemotherapy and 30 received bevacizumab combined with single-agent chemotherapy. Two-drug platinum-based chemotherapy included pemetrexed and cisplatin (PP), gemcitabine and cisplatin (GP), docetaxel and cisplatin (DP) or paclitaxel and carboplatin (TC). Single-agent chemotherapy consisted of pemetrexed (PEM), docetaxel (DTX) or gemcitabine (GEM). All patients were treated intravenously with 7.5 mg/kg bevacizumab every 3 weeks, prior to the chemotherapy (Table 1).

Table 1. Detailed Chemotherapy Regimens in the Study

Chemotherapy		n	Regimens
Platinum-based two-drug chemotherapy	PP	32	Pemetrexed, 500 mg/m^2, IV, day 1 Cisplatin, 75 mg/m^2, IV, day 1 or days 1-3, 3 weeks as a cycle
	GP	7	Gemcitabine, 1000-1250 mg/m^2, IV, day 1, 8 Cisplatin, 75 mg/m^2, IV, day 1 or days 1-3, 3 weeks as a cycle
	DP	6	Docetaxel, 75 mg/m^2, IV, day 1, Cisplatin, 75 mg/m^2, IV, day 1 or days 1-3, 3 weeks as a cycle
	TC	4	Paclitaxel, 175 mg/m^2, IV, day 1 Carbopiatin, AUTC=5, IV, day 1 or days 1-3, 3 weeks as a cycle
Single-agent chemotherapy	PEM	10	Pemetrexed, 500 mg/m^2, IV, day 1, 3 weeks as a cycle
	DTX	16	Docetaxel, 75mg/m^2, IV, day 1, 3 weeks as a cycle
	GEM	4	Gemcitabine, 1 000-1 250 mg/m^2, IV, day 1, 8, 3 weeks as a cycle

AVTC, area under the cure; IV, intravenous

Observational indexes

The disease-control rate (DCR), overall response rate (ORR), progress free survival (PFS), overall survival (OS), and bevacizumab- and chemotherapy-induced toxicities in patients with NSNSCLC treated by bevacizumab concomitant with chemotherapy were analyzed.

Efficacy analysis

The tumor response rate (TRR) was evaluated by radiologic examinations according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and jointly assessed by all authors for each patient (Eisenhauer et al., 2009), but for the small percentage of patients without available radiologic images for our review. The TRR evaluation was conducted based on the doctor-in-charge's response assessment. The ORR was calculated as the percentage of patients with complete response (CR) or partial response (PR). ORR= (complete response (CR)+partial response (PR)) cases/total cases×100%. DCR= (complete response (CR)+partial response (PR)+stable disease (SD)) cases/total cases×100% (Kitamura et al., 2013).

PFS was defined as the duration from the initiation of therapy to the date of PD or death due to any cause. OS was defined as the period from therapy initiation to the date of death due to any cause or the end of this experiment.

Efficacy was usually evaluated every 2 cycles by clinical examination, chest CT-scan, lymph node ultrasound, central nervous system (CNS) imaging with MRI or CT-scans, and bone scintigraphy or 18-FDG PET-scan.

Safety analysis

Toxicity was evaluated weekly. All toxicity events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events CTCAE (Cirillo et al., 2009).

Table 2. Demographic and Baseline Characteristics

Characteristics	n (%)
N 79	
Average age (range)	56 (25-76)
Genders	
Male	51 (64.6)
Female	28 (35.4)
Pathological patterns	
Adenocarcinoma	76 (96.2)
Large cell carcinoma	2 (2.5)
Broncholoalveolar	1 (1.3)
Histologic type	
Well differentiated	38 (48.2)
Moderately differentiated	28 (35.4)
Poorly differentiated	5 (6.3)
Unknown	8 (10.1)
ECOG	
0-1	70 (88.6)
2	9 (11.4)
Surgery history	
No	56 (70.9)
Yes	23 (29.1)
EGFR mutational status	
Mutated	12 (15.2)
Non-mutated	14 (17.7)
Unknown	53 (67.1)
Chemotherapy combined with bevacizumab	
Platinum-based double chemotherapy	49 (62.0)
Single-agent chemotherapy	30 (38.0)
Metastatic locations	
Lung	37 (46.8)
Live	15 (19.0)
Bone	44 (55.7)
Brain	22 (27.8)
Adrenal gland	11 (13.9)
Others	22 (27.8)
Line number of bevacizumab	
1st line	35 (44.3)
2nd line	20 (25.3)
3rd or later line	24 (30.4)

Statistical data analysis

All data was analyzed statistically using SPSS13.0. PFS and OS were estimated by Kaplan–Meier method and analyzed by log-rank test. P-values were derived from two-sided tests. $P<0.05$ was considered to be statistically significant.

Results

Patients' characteristics

From 2009 to 2013, a total of 79 patients with NSNSCLC in Chinese PLA General Hospital received ≥2 cycles of chemotherapy concomitant with bevacizumab treatment. And the detailed characteristics are shown in Table 2.

Efficacy

At the final cutoff date (June 9, 2013), 54 (68.4%) patients had PD and 37 (46.8%) died. For the 79 patients, the ORR was 32.9%, and the DCR was 83.5%, with 26 (32.9%) PR, 40 (50.6%) SD and 13 (16.5%) PD. The ORR of the first-, second-, and third- or later-line treatments were 51.4%, 25.0% and 12.5%, while the DCR were 94.3%, 80.0% and 70.8%, respectively (Table 3).

Table 3. Responses to Treatment

Responses	Patients	CR (%)	PR (%)	SD (%)	PD (%)
1st - line	35	0	18 (51.4)	15 (42.9)	2 (5.7)
2nd - line	20	0	5 (25.0)	11 (55.0)	4 (20.0)
3rd - or later- line	24	0	3 (12.5)	14 (58.3)	7 (29.2)
Overall	79	0	26 (32.9)	40 (50.6)	13 (16.5)

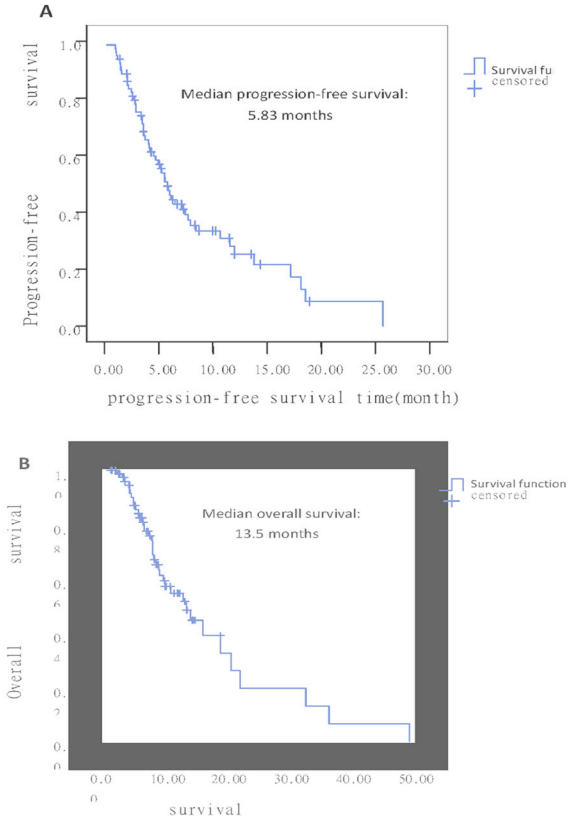

Figure 1. (A) Curve for PFS in Patients with NSNSCLC treated with Bevacizumab-combination Chemotherapy; (B) Curve for OS in Patients with NSNSCLC treated with Bevacizumab Concomitant with Chemotherapy

Table 4 and Figure 1 are showing the results of the analyses of potential predictors for OS and PFS. The median follow-up period for the entire cohort was 26.4 months. The median durations of OS and PFS were 13.50 and 5.83 months, respectively. The median OS (mOS) of patients with the first-, second-, and third- or later-line treatments were 16.17, 10.93 and 8.30 months, while the mPFS were 7.27, 5.90 and 5.17 months, respectively.

Toxicity

All patients had toxicity analysis. The chemotherapy-related adverse events included myelosuppression in 53 (67.1%) patients (neutropenia in 39 (49.4%) and thrombocytopenia in 14 (17.7%)), vomiting in 47 (59.5%), hepatic dysfunction in 9 (11.4%) and renal dysfunction in 6 (7.6%). These events were fully subsided after

Table 4. Survival Analysis

End point	Median follow-up duration* (range)	mPFS (95% CI, month)	mOS (95% CI, month)
1st- line	20.06 (2.80-125.03)	7.27 (4.33-10.22)	16.17 (11.03-21.31)
2nd- line	28.20 (4.77-125.07)	5.90 (2.81-8.99)	10.93 (7.45-14.41)
3rd- or later- line	34.26 (10.40-63.53)	5.17 (2.45-7.89)	8.30 (6.99-9.61)
Overall	26.44 (2.80-125.07)	5.83 (4.80-6.86)	13.50 (8.78-18.22)

*From diagnosis to death or last follow-up date

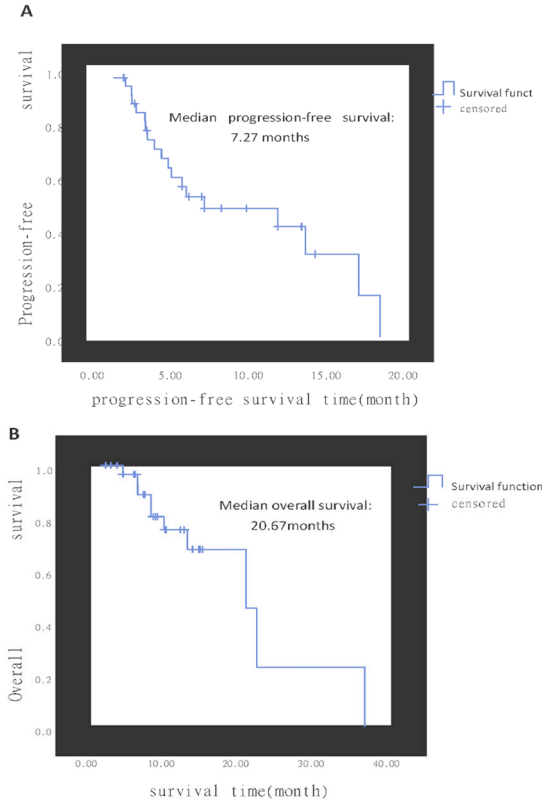

Figure 2. (A) Curve of PFS in Patients with NSNSCLC treated with Bevacizumab combined Cisplatin plus Pemetrexed; (B) Curve of OS in Patients with NSNSCLC Treated with Bevacizumab Combined with Cisplatin Plus Pemetrexed

Table 5. Adverse Responses

Adverse events	Grade 1/2 (%)	Grade 3/4 (%)
Chemotherapy-related		
Neutropenia	23 (29.1)	16 (20.3)
Thrombocytopenia	12 (15.2)	2 (2.5)
Vomiting	44 (55.7)	3 (3.8)
Hepatic dysfunction	9 (11.4)	0
Renal dysfunction	6 (7.6)	0
Bevacizumab-related		
Hypertension	9 (11.4)	2 (2.5)
Bleeding		
Epistaxis	5 (6.3)	1 (1.3)
CNS bleeding	0	0
Digestive bleeding	2 (2.5)	2 (2.5)
Thrombosis	0	0
Proteinuria	1 (1.3)	0
Gastrointestinal perforation	0	0
Reversible posteriorleukoencephalopathy syndrome	0	0

CNS, central nervous system

symptomatic treatments. The 3 most common serious bevacizumab-related adverse events of special interest (any grade) were thromboembolic events, gastrointestinal perforation and reversible posterior leukoencephalopathy syndrome, which were not observed in this study. Since this study aimed at withdrawing the drug immediately after observing hemorrhage or hypertension to ensure the safety, 2 (2.5%) patients stopped using the drug due to severe adverse events. Also, it is worth mentioning that 1 (1.3%) patient died of digestive bleeding after the second cycle, which was considered as a bevacizumab-induced complication (Table 5).

Discussion

Bevacizumab is a standard therapy approved by FDA as the first-line treatment in patients with NSNSCLC. The approval of this compound is mainly based on the supportive results from 2 large randomized phase III clinical trials. In the ECOG 4599 trial, the addition of bevacizumab (15 mg/kg) to carboplatin plus paclitaxel produced a statistically significant and clinically relevant improvement in OS (12.3 vs. 10.3 months), PFS (6.2 vs. 4.5 months) and ORR (35% vs. 15%) (Sandler et al., 2010). The AVAiL trial reported that PFS was significantly extended in NSNSCLC patients treated with bevacizumab (at doses of 7.5 and 15 mg/kg) combined with cisplatin plus gemcitabine (GP), showing that the mPFS values of placebo, low-dose bevacizumab, and high-dose bevacizumab plus GP were 6.1, 6.7 and 6.5 months, respectively (Reck et al., 2009).

An open-label, multicenter, single group, phase IV study (SAIL), which enrolled 2212 patients from 40 countries across 6 continents to evaluate the effects and safety of bevacizumab, indicated that the addition of bevacizumab to the first-line chemotherapy for NSNSCLC was effective and safe (Crino et al., 2010). Based on these data, multiple clinical trials have demonstrated that bevacizumab could improve peoples' PFS and OS (Herbst et al., 2007; Lilenbaum et al., 2008; Reck et al., 2010; Habib et al., 2013). Heist et al's study also proved that bevacizumab concomitant with oxaliplatin plus pemetrexed could yield promising clinical efficacy and manageable toxicity in the treatment of the patients with advanced NSCLC, while Adjei et al found that NSCLC patients could benefit from the treatment with bevacizumab plus pemetrexed with longer mPFS and mOS (Heist et al., 2008; Adjei et al., 2010). A summary of the clinical trials investigating the efficacy of bevacizumab combined with chemotherapy in patients with NSCLC is

Table 6. Summary of Clinical Trials Investigating the Efficacy of Bevacizumab combined with Chemotherapy in Patients with NSCLC

Reference	Phase	Treatment line	Regimen	N[a]	RR (%)	PFS (month)	OS (month)
Johnson[11] 2004	II	1st	TC	32	18.8	TTP 4.2	14.9
			TC+Bev7.5	32	28.1	4.3	11.6
			TC+Bev15	35	35.5	7.4	17.7
Sander[12] 2006	III	1st	TC	433	15.0	4.5	10.3
			TC+Bev15	417	35.0	6.2	12.3
Reck[13, 19] 2009	III	1st	GP	327	20.1	6.1	13.1
			GP+Bev7.5	330	34.1	6.7	13.6
			GP+Bev15	329	30.4	6.5	13.4
Nihos[20] 2012	II	1st	TC	59	31.0	5.6	>22
			TC+Bev	121	60.7	6.9	>22
Habib[21] 2013	Retro	4th line or later	T+Bev	20	25.3	6.4	9.6
Skaff[22] 2009	II	1st	PC+Bev15	25	36	TTP7.25	ND
Waples[23] 2008	II	1st	PO+Bev15	58	26	7.8	16.7
Lilenbaum[24] 2008	II	1st	GO+Bev15	44	43	ND	13.7
Leon[25] 2009	II	1st	NP+Bev15	17	29.4	4.6	ND
Herbst[26] 2007	II	1st	DTX/Pem+Bev15	40	12.5	4.8	12.6
			DTX/Pem+placebo	41	12.2	3.0	8.6
			Erlotinb+Bev15	39	17.9	4.4	13.7
Ferrer[27] 2009	II	1st	PD+Bev15	46	63	7.8	13.5
Crino[28] 2010	III	1st	Chem+Bev7.5/15	2212	51	7.8	14.6
Fischbach[29] 2009	III	1st	Chem+Bev7.5/15	1758	ND	6.7	ND
Adjei[30] 2010	II	2nd	Pem+Bev15	48	10	4.0	8.6
Heist[31] 2008	II	2nd	PO+Bev15	34	27	5.8	12.5

*[a]Patients evaluable for efficacy; Bev: bevacizumab (7.5mg/kg, 15mg/kg), PC: Pemetrexed+Carbopiati; PO: Pemetrexed+Oxaliplatin; GO: Gemcitabine+Oxaliplatin; NP: Vinorelbine+Cisplatin; ND: no data available; RR: response rate; TTP: time to progression

shown in Table 6. Although large numbers of patients have been enrolled in clinical trials and positive results were obtained, the clinical trials performed in our country had mostly enrolled a limited number of participants (Crino et al., 2010). Therefore, the efficacy of bevacizumab in our country still needs to be further investigated.

The effect of cisplatin, pemetrexed, and bevacizumab (PPB regimen) combination treatment in Chinese patients with advanced NSNSCLC has not been reported. However, in this retrospective study, ORR was 32.9% and the DCR was 83.5%for all patients, while mPFS and mOS were 5.83 and 13.50 months, respectively. Of the 79 patients, 32 (40.5%) accepted the PPB regimen. And of the 32 patients, 11 (34.4%) were treated with bevacizumab combined with cisplatin plus pemetrexed as the first-line treatment, 20 (62.5%) with the second-line treatment and only 1 (3.1%) with the third line treatment. However, at the final cutoff date (June 9, 2013), of the 32 patients in PPB subgroup, 19 had PD (59.4%) and 10 (31.3%) died, 15 (46.9%) had PR and 14 (43.8%) achieved SD, exhibiting an ORR of 46.9% and the median duration of PFS and OS being 7.27 and 20.67 months, respectively (Figure2).

The current study demonstrated that patients in PPB regimen subgroup benefited clinically more than the others. That may have been caused by the small sample size and, also, perhaps as a result of the fact that only 1 patient was treated with the third-line treatment, which needed to be further observed. Therefore, this retrospective study concluded that bevacizumab concomitant with chemotherapy was effective in Chinese patients with advanced NSNSCLC with tolerable and manageable adverse events.

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