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Original Article

Hypertension does not influence response to EGFR targeted therapy in patients with advanced non-small-cell lung cancer

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Abstract: Hypertension is prevalent in patients with epidermal growth factor receptor (EGFR) mutated non-small-cell lung cancer (NSCLC). The aim of this study was to illuminate the impact of hypertension on first-line targeted therapy in patients with advanced NSCLC. A total of 102 patients with EGFR mutations were included in this study. Patients were retrospective divided into two groups according to the status of hypertension. All patients received EGFR targeted therapy on standard dose as recommended by clinical guidelines. The primary end point was progression-free survival (PFS). Secondary end points were objective response rate (ORR), disease control rate (DCR) and toxicity. The relationships between different groups and patients characteristics were performed using Pearson's Chi-square test or Fisher's exact test. Logistic regression was performed between patient characteristics and treatment efficacy. Estimates of PFS and OS were calculated using the Kaplan-Meier method and two-sided 95% confidence interval were obtained. A two-sided log-rank test was used to compare PFS between the two study groups. The clinical characteristics for first-line EGFR-TKIs treatment were well balanced between NSCLC patients with or without hypertension. The objective response rate (ORR) in hypertension patients was 62.9%, median progression-free survival (PFS) was 9.4 months (95% CI, 7.3 to 11.6 months) and a 1-year PFS rate was 31.4%, similar to that of ordinary NSCLC patients. Toxicities were generally manageable in the two groups, which seldom produced grade 3 or higher adverse events. Therefore, hypertension did not decrease the therapeutic efficacy or increase the toxicity of EGFR-TKIs for patients with advanced NSCLC. Further studies are suggested to identify the impact of hypertension on such circumstance.

Keywords: Hypertension, targeted therapy, first-line therapy, non-small-cell lung cancer (NSCLC)

Introduction

Non-small-cell lung cancer (NSCLC) is one of the most common cancers worldwide [1]. As patients diagnosed with advanced NSCLC are primarily at an elder age and are often heavy smokers, other common diseases such as hypertension are usually coexisted in the same patient population [2]. In addition, the prevalence of hypertension in patients with advanced NSCLC was similar to that in the ordinary population [3].

The presence of hypertension prior to treatment may predict poor prognosis of cancer patients, due to increased risk of myocardiopathy caused by chemotherapeutic drugs and angiogenesis inhibitors [4, 5], which further increase blood pressure during consecutive treatment among such patients [6]. To date, there have been many reports concerning the relationship between treatment-related hypertension and antitumor efficacy in advanced NSCLC. One report revealed that early treatment-related blood pressure increases did not predict clinical benefit from bevacizumab based on efficacy outcomes, nor did it have any prognostic importance for patients with advanced NSCLC [7].

Previous reports showed that patients harboring EGFR gene mutations could benefit from treatment with tyrosine kinase inhibitors (TKIs) such as erlotinib [8], icotinib [9], gefitinib [10]

Table 1. Patient Characteristics

Characteristic	Hypertension group (n=35)	Ordinary group (n=67)	*P* value
Age			
Median	66	60	
Range	36 to 82	27 to 83	
Years of diagnosis			
18-39	1 (2.9%)	6 (9%)	0.05
40-64	14 (40%)	39 (58.2%)	
65-85	20 (57.1%)	22 (32.8%)	
Sex			
Male	15 (42.9%)	27 (40.3%)	0.8
Female	20 (57.1%)	40 (59.7%)	
ECOG PS			
0-1	24 (64.9%)	52 (77.6%)	0.48
2	8 (21.6%)	9 (13.4%)	
3 or more	3 (13.5%)	6 (9%)	
Lung stage			
Stage IIIB or less	1 (2.9%)	2 (3%)	1.0
Stage IV	34 (97.1%)	65 (97%)	
Brain Metastasis			
Yes	11 (31.4%)	30 (44.8%)	0.19
No	24 (68.6%)	37 (55.2%)	
Smoking			
Yes	9 (25.7%)	13 (19.4%)	0.46
No	26 (74.3%)	54 (80.6%)	
EGFR mutation status			
Exon 19 del	17 (48.9%)	29 (43.2%)	0.89
Exon 21 L858R	16 (45.7%)	32 (47.8%)	
Exon 18 G719X	1 (2.9%)	2 (3%)	
Other	1 (2.9%)	4 (6%)	
Durgs			
Gefitinib	16 (45.7%)	35 (52.2%)	0.7
Erlotinib	4 (11.4%)	8 (11.9%)	
Icotinib	15 (42.9%)	22 (32.9%)	
Afatinib	0	2 (3%)	

and afatinib [11], with a median progression-free survival (PFS) of 9-13 months and a median overall survival (OS) of 2-3 years. The side effects of EGFR-TKIs are different from chemotherapy and anti-angiogenesis therapy [12]. If hypertension could decrease the efficacy of targeted therapy, or increase the toxicity of EGFR-TKIs, it would be unfortunate for NSCLC patients. Hence, to investigate the clinical connection of hypertension and EGFR-TKIs treatment is meaningful.

The targeted therapeutic drugs of advanced NSCLC referred above is extensively used in the clinic, which exhibit almost the same treatment effect [13, 14]. Hence, the efficacy of EGFR-TKIs for patients with hypertension in our hospital was retrospectively analyzed, with the aim to illuminate the relationship of hypertension and targeted therapy in advanced NSCLC.

Patients and methods

Eligibility

A retrospective analysis of EGFR mutated NSCLC patients with or without hypertension was conducted at Dongguan People's Hospital, Southern Medical University from May 2014 to December 2017. The eligible patients were ≥ 18 years old, with cytological or histological confirmation of stage IIIB (with pleural effusion) and stage IV EGFR gene mutated NSCLC (The International Association for the Study of Lung Cancer 7th edition of Tumor Node Metastasis Staging classification) and had never received any antitumor regimens before. EGFR mutations were identified in tumor tissues using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (Sanger), the scorpion amplification refractory mutation system method (ARMS) or next-generation sequencing technology (NGS). Patients who were during the pregnant, allergic to targeted drugs, or had primary organ failure were excluded from our analysis. Patients whose clinical information could not be completely obtained were also excluded from this study.

Treatment

This study was approved by local ethics committees and was conducted according to the Declaration of Helsinki. Patients provided informed written consent. A total of 102 patients with EGFR mutations were included in this study. Patients were retrospective divided into two groups according to the status of hypertension, regardless of age, sex, physical scores, or treatment agents. 35 patients were

Table 2. Efficacy Results

Variable	Hypertension group (n=35)		Ordinary group (n=67)		*P* value
	No.	%	No.	%	
Response					
PR (%)	22	62.9	34	50.8	
SD (%)	8	22.9	23	34.3	
PD (%)	5	14.2	10	14.9	
Response rates, %	62.9		50.8		*0.25*
95% CI	46.6 to 79.1		38.7 to 62.8		
Disease control rates, %	85.7		85.1		0.93
95% CI	74.1 to 97.5		76.5 to 93.7		
Median PFS (months)	9.4		7.9		0.66
95% CI	7.3 to 11.6		4.3 to 11.5		
1 year PFS rates (%)	31.4		29.9		0.21
Median PFS in BM patients (months)	8.4		6.2		0.87
95% CI	5.9 to 10.8		2.8 to 9.6		

diagnosed with hypertension before targeted treatment. All patients received EGFR-TKIs on standard dose as recommended by clinical guidelines, before unendurable toxicity or disease progression occurred.

Data collection

The clinical data of patients in our studies was collected carefully. All patients had an ECOG PS of 0 to 3. Patient history, physical examination and complete blood work were recorded at baseline and before EGFR-TKIs treatment. Tumor response was evaluated by computed tomography scans according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Disease control was defined as complete remission (CR), partial response (PR) or stable disease (SD). Patients who had a progression disease caused by EGFR-TKIs treatment were defined as progression disease (PD). Toxicities were recorded and classified in the light of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Statistical Analysis

The primary end point was PFS, defined as time between the start of the treatment and disease progression or death, with censoring for patients alive without progression at last contact. The secondary end points were objective response rate (ORR), disease control rate (DCR) and toxicity. The cutoff date for PFS data was June 28, 2018, when the last patient had initiated his treatment for 6 months. By that time, enough data was collected to analyze the efficacy and toxicities of study arms.

Statistical analysis was performed by Statistical Product and Service Solutions (SPSS) 22.0 software. Relationships between different groups and patients characteristics were performed using Pearson's chi-square test or Fisher's exact test. Logistic regression was performed between patient characteristics and treatment efficacy. Estimates of PFS and OS were calculated using the Kaplan-Meier method and two-sided 95% confidence interval were obtained. A two-sided Log-rank test was used to compare PFS between the two study groups.

Results

Patient characteristics and treatment

The clinical characteristics of these patients for first-line EGFR-TKIs treatment are detailed in **Table 1**. There were no statistically significant differences between hypertension patients and ordinary patients with advanced NSCLC. The median age of hypertension patients was 66 years (range, 36-82 years) and 57.1% patients were women, and that of ordinary patients free of hypertension were 60 years (range, 27-83 years) and 59.7%. Most of the patients in two groups had a performance status of 0-1 score (64.9% versus 77.6%) and stage IV disease (97.1% versus 97%). In addition, the majority of the patients were never smokers (74.3% versus 80.6%) and had sensi-

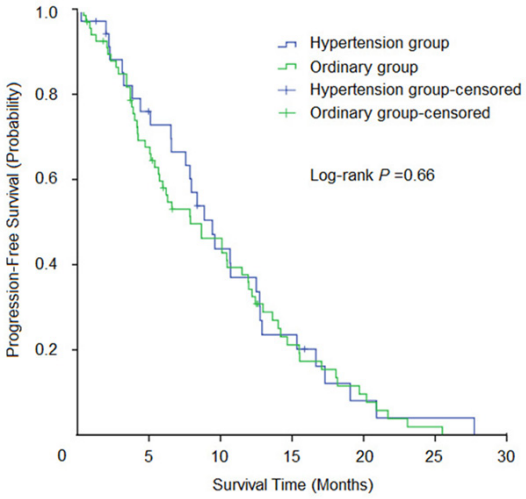

Figure 1. Kaplan-Meier curves for progression-free survival (PFS).

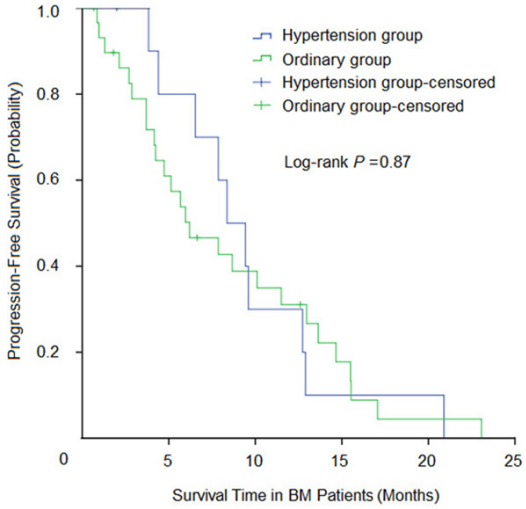

Figure 2. Kaplan-Meier curves for progression-free survival (PFS) of patients with brain metastasis.

tive EGFR gene mutations (97.1% versus 94%). The most common mutation was the L858R mutation in exon 21 and deletion in exon 19, about 74.3% and 80.6% in the two groups, respectively. All patients had never received any antitumor therapy before the initial therapy. In the study, these patients received EGFR-TKIs, gefitinib (250 mg/day), erlotinib (150 mg/day), icotinib (375 mg/day) or afatinib (40 mg/day), until disease progression, unacceptable toxicity or economic factors. Computed tomography (CT) and magnetic resonance imaging (MRI) were conducted routinely to evaluate the efficacy of EGFR-TKIs treatment.

Efficacy

As is illustrated in **Table 2**, objective responses of EGFR-TKIs therapy were observed in 22 of 35 patients in the hypertension patients arm (62.9%; 95% CI, 46.6 to 79.1) and in 34 of 67 patients in the ordinary patients arm (50.8%; 95% CI, 38.7 to 62.8) (P=0.25). DCR of these two groups were 85.7% (95% CI, 74.1 to 97.5) and 85.1% (95% CI, 76.5 to 93.7) (P=0.93), respectively. The median PFS was 9.4 months (95% CI, 7.3 to 11.6 months) in the hypertension patients arm and 7.9 months (95% CI, 4.3 to 11.5 months) in the counterpart arm (P=0.66) (**Figure 1**). The 1-year PFS rate were 31.4% and 29.9%, respectively (P=0.21) (**Table 2**). For patients with brain metastasis (BM), the median PFS of such patients was 8.4 months (95% CI, 5.9 to 10.8 months) and 6.2 months (95% CI, 2.8 to 9.6 months) (P=0.87) (**Figure 2**), respectively. On the whole, there were no statistically differences in therapeutic efficacy of the two patient groups.

Adverse events

The main toxicities possibly related to therapy are listed in **Table 3**. Adverse events of EGFR-TKIs were generally mild, ranging from grade 1 to grade 2. No patients in the study had severe adverse events. The most common grade 1/2 adverse events of both groups were non-hematologic toxicities, including rash, raised aminopherase, anorexia and fatigue. There were 11 episodes of grade 3/4 adverse events in the hypertension patients arm, as compared with 18 episodes in the ordinary patients arm (P=0.27). Grade 3/4 hematologic toxicities observed in the study were rash (11.4%), diarrhea (5.7%), dyspnea (5.7%), raised aminopherase (2.9%), fatigue (2.9%) and hemorrhage (2.9%) in the hypertension patients arm and rash (11.9%), diarrhea (8.9%), dyspnea (4.5%) and fatigue (1.5%) in the counterpart arm.

Discussion

Standard first-line treatment for patients with EGFR mutated advanced NSCLC was mainly single agent such as gefitinib, erlotinib or icotinib. In the majority of studies concerning EGFR targeted therapy, little attention is payed to those patients with hypertension, as compared in the antiangiogenic therapy of advanced NSCLC [15, 16]. As hypertension and lung can-

Table 3. Treatment related toxicities in the two treatment groups.

Toxicity	Total (n=102)		Hypertension group (n=35)		Ordinary group (n=67)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Rash	30 (29.4%)	12 (11.8%)	11 (31.4%)	4 (11.4%)	19 (28.4%)	8 (11.9%)
Pruritus	14 (13.7%)	0	5 (14.3%)	0	9 (13.4%)	0
Dizziness	11 (10.8%)	0	3 (8.6%)	0	8 (11.9%)	0
Fever	10 (9.8%)	0	3 (8.6%)	0	7 (10.4%)	0
Diarrhea	14 (13.7%)	8 (7.8%)	7 (20%)	2 (5.7%)	7 (10.4%)	6 (8.9%)
Fatigue	18 (17.6%)	2 (1.9%)	5 (14.3%)	1 (2.9%)	13 (19.4%)	1 (1.5%)
Nausea	17 (16.7%)	0	6 (17.1%)	0	11 (16.4%)	0
Vomiting	16 (15.7%)	0	6 (17.1%)	0	10 (14.9%)	0
Anorexia	29 (28.4%)	0	10 (28.6%)	0	19 (28.4%)	0
Raised aminopherase	3 (29.4%)	1 (1%)	8 (22.9%)	1 (2.9%)	22 (32.8%)	0
Dyspnea	13 (12.7%)	5 (4.9%)	3 (8.6%)	2 (5.7%)	10 (14.9%)	3 (4.5%)
Hemorrhage	6 (5.9%)	1 (1%)	2 (5.7%)	1 (2.9%)	4 (5.9%)	0

cer share some similar risk factors, hypertension is very prevalent in patients diagnosed with advanced NSCLC. So far, treatment-related hypertension has been investigated extensively, due to the same wide use of angiogenesis inhibitors such as bevacizumab [17, 18]. However, there are fewer studies concerning the efficacy of EGFR-TKIs in cancer patients who already suffered from hypertension.

In this study the relationship between hypertension and therapeutic efficacy in treatment naïve NSCLC patients with EGFR gene mutation was evaluated. This study showed encouraging findings in hypertension patients, with ORR 62.9%, median PFS 9.4 months and 1-year PFS rate 31.4%, which is similar to that of ordinary NSCLC patients who did not suffered from hypertension simultaneously (**Table 2** and **Figure 1**). Toxicities were also manageable, which rarely produced grade 3 or higher adverse events, nor did increased side effect be observed in the hypertension group (**Table 3**). All results were consistent with previous studies of EGFR mutated advanced NSCLC patients. As the number of patients in this study was relatively small, additional studies are needed to further illuminate the efficacy of EGFR-TKIs in hypertension patients.

Patients with brain metastasis (BM) were also investigated in this retrospective analysis separately. About 20-40% patients with advanced NSCLC will develop brain metastasis [19], with a median overall survival only about 3-6 months before the era of precision medicine. The poor prognosis is mainly caused by blood-brain barrier [20], which limited influx of antitumor drugs such as chemotherapeutic agents, angiogenesis inhibitors and even EGFR-TKIs. However, some studies showed that the integrity of blood-brain barrier was disrupted in patients with brain metastasis and that cerebral vessels were dilated and dividing endothelial cells were detected [21]. Coincidently, dysfunction of vascular endothelium in hypertension patients were revealed in previous studies [22, 23], which also showed morphology alteration in endothelial and vascular smooth muscle cells during hypertension development.

As the role of EGFR-TKIs for NSCLC patients with hypertension and brain metastasis is still uncertain, elaboration of the relationship between the efficacy of targeted therapy and such special patients is necessary and important. In the study, a total of 41 appropriate NSCLC patients were analyzed, with 11 hypertension cases. The median PFS of such patients was 2.2 months longer than that of ordinary NSCLC patients, yet did not showed any statistical significance among the two different patient groups (**Table 2** and **Figure 2**). One probable reason was that the number of patients enrolled in this study was too small. Therefore, further study is needed to evaluate the efficacy of EGFR-TKIs in the treatment of brain metastatic NSCLC with hypertension prior to antineoplastic therapy.

In conclusion, this study is the largest investigation to date to compare the efficacy and toxicity

of EGFR-TKIs in advanced NSCLC patients with different blood pressure status when diagnosed. Hypertensive patients treated with EGFR-TKIs had similar response rate and PFS to ordinary NSCLC patients. Toxicities were also not aggravated. Importantly, for patients with brain metastasis, hypertension did not decrease the efficacy of EGFR-TKIs. These results may give hypertensive patients more confidence to accept EGFR-TKIs treatment for advanced NSCLC. In the future, randomized studies are needed to eventually identify the impact of hypertension on targeted therapy of patients with advanced NSCLC.

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Disclosure of conflict of interest

None.

Abbreviations

NSCLC, non-small-cell lung cancer; PFS, progression-free survival; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SPSS, Statistical Product and Service Solutions; ARMS, the scorpion amplification refractory mutation system method; NGS, next-generation sequencing technology; ECOG, Eastern Cooperative Oncology Group; PS, physical score; CT, Computed tomography and MRI, magnetic resonance imaging; BM, brain metastasis.

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