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Original Article

Curative effect analysis of different treatments for gefitinib-resistance advanced non-small cell lung cancer patients

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Abstract: Objective: Gefitinib is effective epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) for advanced non-small cell lung cancer (NSCLC) patients, but with the drug use, inevitable gefitinib-resistance and severe complications were observed and resulted in failure treatments. The purpose of the present study was to investigate the curative effect of different treatment of navelbine plus cisplatin in combination with gefitinib and gefitinib single on gefitinib-resistance advanced NSCLC patients. Methods: Total Of 120 patients acquired gefitinib-resistance NSCLC patients treated in Taian City Central Hospital of Shandong province from May, 2010 to June, 2014 were incorporated in our study according to the inclusion and exclusion criteria. The patients were divided into chemotherapeutical group and gefitinib group and the mean follow-up was 12 months (6-39 months), the information of patients was recorded as gender, age, smoking, complications, hepatic metastasis, bone metastasis, brain metastasis and acquired chemotherapy or not. Chi-square test and t-test were performed to analyzed collection data, Log-rank was analyzed significance of survival time among groups and Cox regression was evaluated independent risk factors of survival analysis. Results: The survival time of chemotherapy group was significantly longer than gefitinib group; the survival time among the two groups was 29.06 and 15.23 months ($P<0.05$), respectively. Multivariate Cox regression analyzed that lesion's metastasis (hepatic metastasis, bone metastasis and brain metastasis) and acquired chemotherapy were independent risk factors influence on patients overall survival time; gender, age, smoking, complications had no significance influence on survival time between the two groups. Conclusion: Lesion's metastasis and acquired chemotherapy were independent risk factors influence on patients' overall survival time and the survival time of chemotherapy group was significantly longer than gefitinib group.

Keywords: Non-small cell lung cancer, metastasis, chemotherapy, overall survival, gefitinib-resistance, progression-free survival

Introduction

Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer [1], most of patients have been found distal metastasis at the time of diagnosis. The 5-year survival rate is less than 15% [2]. At present, the standard first-line and second-line chemotherapy treatments are the main method of inhibiting tumor cell growth of advance NSCLC patients, but the curative effect is limited and with the side effect of high toxicity.

In recent years, the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) was applied for advanced NSCLC patients as a clinically therapeutic measure, which greatly improved the patients' survival time and life quality [3, 4]. The gefitinib treatments can significantly prolonged survival time of patients with advanced NSCLC had been confirmed. Through clinical trials observation, gefitinib treatments were objectively effective for 12-18% patients, after platinum-based chemotherapy treated advanced NSCLC failure; the median survival period was almost 7 months [5, 6].

Gefitinib is the first EGFR-TKI applied to clinical treatment, characterized by light side effect

Table 1. Patients' demographics

Parameter	CG	GG	χ^2/t-test	*P*-value
Gender				
Male	36	31	3.39	0.06
Female	24	29		
Age (year)	58.11±12.98	63.54±12.02	1.43	0.16
Smoking				
with	28	21	0.31	0.58
without	32	39		
Complications				
with	41	29	0.25	0.61
without	19	31		
Hepatic metastasis				
with	28	25	2.98	0.08
without	32	35		
Bone metastasis				
with	37	28	2.98	0.08
without	23	32		
Brain metastasis				
with	20	22	0.24	0.53
without	40	38		
Total	60	60		

χ^2: chi-square; CG: chemotherapy group; GG: gefitinib group; P<0.05 was statistical significance.

and good tolerance [7], the curative effect has been recognized for the treatment of NSCLC. But patients acquired gefitinib treatment would be found gefitinib resistance, clinically characterized by lesions growth and metastasis, according to the clinically observed [8, 9].

Currently, the mechanism of NSCLC patients obtained drug-resistance after gefitinib treatment is not elucidated. The EGFR T790M mutation and MET amplification are the most common EGFR-TKI acquired resistance mechanisms, accounting for 60% cases [10, 11]. EGFR T790M mutation, 2369 nucleotide site of 20 exon, cytosine replaced by thymine lead to threonine replaced by methionine, the change may inhibit EGFR binding with TKI resulted in acquired resistance finally [12, 13]. In addition, c-Met related to acquired resistance was reported, c-Met gene amplification activated ErbB3/PI3K/AKT signaling pathway induced gefitinib resistance [14]; c-Met encoded hepatocyte growth factor (HGF) acted on GAB1 and induced EGFR positive mutation of lung adenocarcinoma cell resistance on EGFR-TKI [15].

Various dosage regimes to overcome EGFR-TKIs resistance have been studied in preclinical or clinical trials, consisting of afatinib therapy [16], pemetrexed plus platinum in combination with gefitinib [17], gefitinib plus the MET TKI crizotinib [18], pemetrexed in combination with EGFR-TKIs [19].

In this study, dosage regimes of navelbine plus cisplatin in combination with gefitinib or gefitinib single were given to gefitinib-resistance advanced NSCLC (GR-ANSCLC) patients; we analyzed the curative effect of different treatments. The study displayed that lesion's metastasis (hepatic metastasis, bone metastasis and brain metastasis) and acquired chemotherapy are independent risk factors influence on gefitinib-resistance NSCLC patients' overall survival, curative effect of chemotherapy group is more obvious than gefitinib group.

Material and methods

Patients

120 patients of gefitinib-resistant advanced NSCLC were incorporated into our study from May 2010 to June 2014, according to inclusion and exclusion criteria; the patients were divided into chemotherapy group and gefitinib group, then preformed to different treatments and the patients' information contained gender, age, smoking, complications, hepatic metastasis, bone metastasis, brain metastasis and chemotherapy acquired were collected.

Inclusion and exclusion criteria

Inclusion criteria covered following: 1. NSCLC were confirmed by histology and (or) cytology examinations; 2. No limitations on acquired radiotherapy, chemotherapy or other treatments ever; 3. Patients were acquired gefitinib treatments ever; 4. Patients with organ metastasis (liver, bone or brain) and kept in a stable condition at least half of a year; 5. Routine blood examination, liver and kidney function were normal.

Exclusion criteria contained the following: 1. Instability of systemic diseases, including of pulmonary infection, hypertension of level 4, heart disease and liver and kidney dysfunction;

Table 2. The significance analysis of curative effect between chemotherapy group and gefitinib group

Parameter	No.	PR	SD	PD	RR (%)	*P*-value
Curative effect						
CG	41	23	14	4	23 (56%)	>0.05 (0.06)
GG	37	20	11	6	20 (54%)	
Age (year)						
CG	46	28	24	9	28 (60.8%)	>0.05 (0.35)
GG	52	32	17	11	32 (61.5%)	
Smoking						
CG	37	27	10	23	27 (72.9%)	>0.05 (0.52)
GG	49	18	26	16	18 (36.7%)	
Complication						
CG	29	24	15	21	24 (82.7%)	>0.05 (0.23)
GG	41	31	19	10	31 (75.6%)	
Bone metastasis						
CG	31	17	10	4	17 (54.8%)	>0.05 (0.16)
GG	28	14	12	2	14 (50%)	
Hepatic metastasis						
CG	39	21	12	6	21 (53.8%)	>0.05 (0.08)
GG	32	16	10	6	16 (50%)	
Brain metastasis						
CG	26	11	8	7	11(42.3%)	>0.05 (0.07)
GG	35	17	11	7	17 (48.5%)	

No: the number of patients; CG: chemotherapy group; GG: gefitinib group; PR: partial response; SD: stable diseases; PD: progression diseases; RR: CR + PR; P<0.05 was statistical significance.

Table 3. The change analysis of overall survival among before drug-resistance and after drug-resistance groups

Groups	After drug-resistance	
	OS	*P*-value
CG	29.06	0.00
GG	15.23	

CG: chemotherapy group; GG: gefitinib group; OS: overall survival.

2. Patients were highly sensitive to gefitinib with complications; 3. Pateints with pulmonary fibrosis; 4. Clinical staging was indistinct or cases lack of specific clinical data.

Dosage regimen

120 patients of gefitinib-resistance advanced NSCLC were divided into chemother-apy group and gefitinib group. Dosage regimen of chemotherapy group was given four weeks Navelbine plus Cisplatin (NP) chemotherapy and followed oral administration of gefitinib four weeks: at the 1st, 8th, 15th, 22th, 29th days was given intravenous injection Navelbine (Vinorelbine Bitartrate Injection, Pierre Fabre Medicament, 10 mg/ml, France) for 25-30 mg/m^2; at the 1st and 29th days, was given Cisplatin (Biovalley, Yunnan, 10 mg, China) for 120 mg/m^2; then given 250 mg/d gefitinib (Iressa, AstraZeneca, UK) for four weeks, this treatment was repeated until disease progression. Dosage regimen of gefitinib group was after drug withdrawal for 1 month, gefitinib was given oral administration of 250 mg/d.

Assessment criteria

Objective response rate was evaluated according to the RECIST criteria [20]. The best overall response can be divided into complete response (CR), partial response (PR), stable diseases (SD) and progression diseases (PD). Progression-free survival (PFS) were defined as the time interval between chemotherapy group or gefitinib group acquired treatments for first time and disease progression or death for any reason observed; overall survival (OS) was defined as the time interval between chemotherapy group or gefitinib group acquired treatments for first time and death for any reason observed; censored data was defined as that in the mean follow-up 12 months, cases of patients were still alive or died of other diseases.

Ethic

The study was approved by the Ethic Committee of Taian City Central Hospital of Shandong province. The ethics committee approved the relating screening, inspection, and data collection of the patients. All of research objects, 120 patients incorporated into the study fully understood the whole treatment process and signed informed consent.

Statistics analysis

Differences in the progression-free survival among groups given different dosage regimen were calculated with log-rank test of Kaplan-

Table 4. Cox analysis of multivariate effect of overall survival

Parameter	Wald	OR	95% CI	*P*-value
Metastasis	5.025	0.224	0.208-1.974	<0.05 (0.015)
Chemotherapy	15.291	4.686	2.234-13.479	<0.05 (0.034)
Age	1.127	2.178	1.479-2.893	>0.05 (0.821)
Gender	4.527	2.659	1.573-3.654	>0.05 (0.637)
Smoking	3.039	1.647	0.356-2.176	>0.05 (0.253)

Metastasis: consist of hepatic metastasis, bone metastasis and brain metastasis; Chemotherapy: acquired Chemotherapy treatment or not; CI: confidence interval; OR: odds ration; P<0.05 was statistical significance.

Meier survival analysis. Multivariate Cox regression was used to analyze the risk factors of survival time. *P*<0.05 was statistical significance; statistical analysis was performed using SPSS version 18.0. Measurement data were described as means ± standard deviation.

Results

The basic information of patients

Total of 120 patients incorporated into ours study according to Inclusion and exclusion criteria were divided into chemotherapy group and gefitinib group. There were 36 males and 24 females were included in the chemotherapy group and the age is 58.11±12.98 years; 31 males and 29 females were in gefitinib group, the age was 63.54±12.02 years. As **Table 1** Shown, the differences of smoking, hepatic metastasis, bone metastasis, brain metastasis between chemotherapy group and gefitinib group were not statistically significant.

The different curative effect between chemotherapy group and gefitinib group

Chemotherapy group and gefitinib group were given chemotherapy for one cycle then given gefitinib, gefitinib group were given gefitinib single. The curative effects were observed and evaluated. As **Table 2** Shown, complete responses (CR) of patients were not observed among total of 120 patients. 23 cases of partial response (PR, 56.0%), 14 cases of stable diseases (SD, 34.1%), 4 cases of progression diseases (PD, 8%) were observed in and the effect rate of RR (CR + PR) of chemotherapy group was 56.0%. 20 cases of PR (56.0%), 11 cases of SD (34.1%), 6 cases of PD (8%) were observed in 37 patients gefitinib group and the effect rate of RR (CR + PR) of gefitinib group was 54.0%. The differently curative effect between chemotherapy group and gefitinib group were not statistically significant (P>0.05), as **Table 2** shown.

Chemotherapy treatment effect on the overall survival time after drug resistance

As **Table 3** shown, the mean survival time after gefitinib-resistance of chemotherapy group was 29.06±1.78 months and gefitinib group was 15.23±1.25 months, there was significant difference between chemotherapy group and gefitinib group (*P*<0.05).

Cox multivariate regression analysis

The mean follow-up was 12 months of chemotherapy group and gefitinib group, the multiple factors of lesion's metastasis (hepatic metastasis, bone metastasis and brain metastasis), acquired chemotherapy, age, gender and smoking were analyzed using Cox regression. As **Table 4** shown, the overall survival of both chemotherapy group and gefitinib group was influenced by the risk factor of metastasis, acquired chemotherapy treatment or not, the difference was statistically significant *(P*<0.05), compared with that age, gender and smoking are less influence of overall survival, the difference was not significant (*P*>0.05).

Risk factors effect on overall survival time

The studies displayed that lesions metastasis and acquired chemotherapy or not are the risk factors of overall survival time of gefitinib-resistance advanced NSCLC patients. Progression-free survival (PFS) curves of the risk factors of lesion's metastasis (**Figure 1**) and acquired chemotherapy (**Figure 2**) were analyzed by Kaplan-Meier method, as the figures shown, progression-free survival rate of chemotherapy group was obviously higher than gefitinib group with a significant difference (P<0.05).

Discussion

In this study, 120 advanced NSCLC patients acquired gefitinib-resistance were divided into chemotherapy group and gefitinib group then followed up for mean 12 months. Chemotherapy

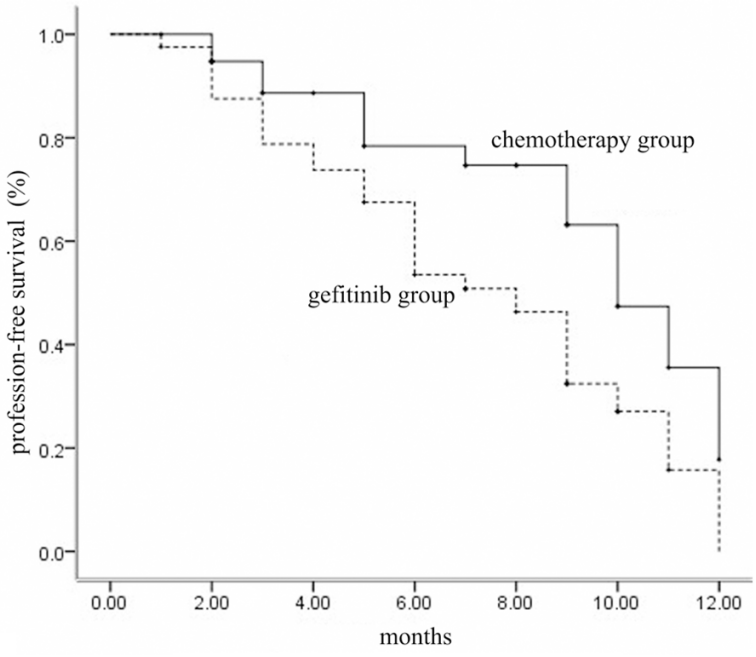

Figure 1. Progression-free survival (PFS) curves of the risk factors of lesion's metastasis. Kaplan-Meier was performed to analyze PFS curves between gefitinib group and chemotherapy group.

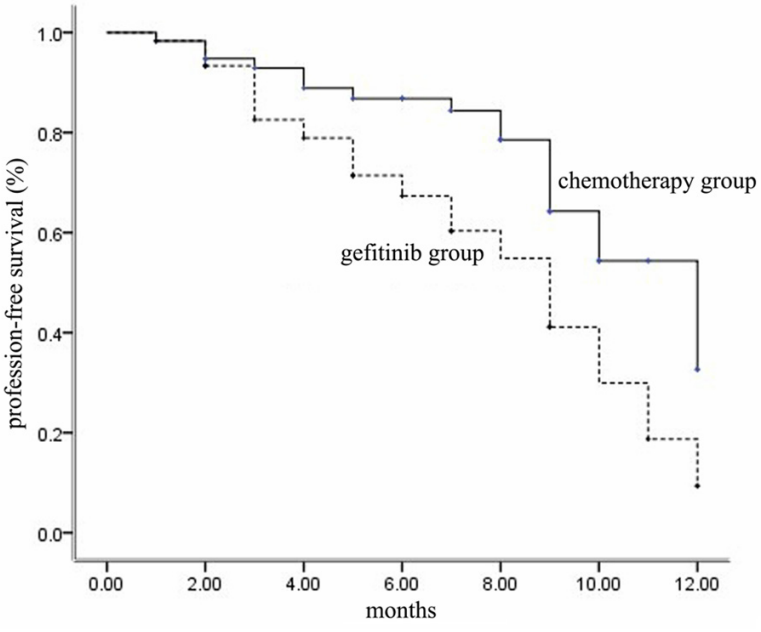

Figure 2. Progression-free survival curves of the risk factors of acquired chemotherapy. Kaplan-Meier was performed to analyze PFS curves between gefitinib group and chemotherapy group.

group were given treatment for NP chemotherapy in combination with gefitinib; gefitinib group were treated for after drug withdrawal one month then given gefitinib. statistical analysis displayed the survival time of chemotherapy group was significant longer than gefitinib group, the objective effective rate of chemotherapy group and gefitinib group was 56% and 54%, respectively, far higher than 11.8% and 18.4% of clinical trial were reported [21].

The study demonstrated that gefitinib group of patients with risk factor of gender, smoking, complications and metastasis in patients had good curative effect, but there was no statistical difference between chemotherapy groups and gefitinib group. On the analysis of the risk factors related to the cases of two groups, age, smoking, gender, metastasis and acquired chemotherapy were potential risk factors predicted the curative effect among chemotherapy group and gefitinib group, through the multivariate analysis of our study, multi-metastasis and acquired chemotherapy after gefitinib-resistance obtained were independent risk factors influence on survival time.

It is reported that the risk factors influence on survival time after gefitinib-resistance obtained shown that there was no statistically significant difference of risk factors consist of gender, age, smoking, whether used chemotherapy drugs, whether with lesion's metastasis for progression-free survival time between chemotherapy group and gefitinib group [21-25]. But in our study, through the observations for gefitinib-resistance advanced NSCLC patients for mean follow-up 12 months, we found that multiple metastasis and acquired chemotherapy were independent risk factors influence on progression-free sur-

vival time. Kaplan-Meier analysis were performed and indicated that progression-free survival rate was higher of chemotherapy than gefitinib group, suggest that better prognosis than gefitinib group.

To conclude, our study displayed that gefitinib-resistance advanced NSCLC patients obtained longer survival time in chemotherapy group acquired chemotherapy and oral administration gegitinib than gefitinib group given gefitinib single.

But there are limitations in this study, the sample size was small, and lack of TNM staging of tumor and EGFR mutation detection. In the prospective study, multi-cancer and larger size samples will be analyzed, through risk factors analysis effect on clinical dosage regimen to found reasonable treatment for gefitinib-resistance advanced NSCLC patients, and aim to allow gefitinib-resistance advanced NSCLC patients obtain longer survival time.

Disclosure of conflict of interest

None.

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