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Application of afatinib combined with np regimen in the treatment of stage iv non-small cell lung cancer and its effect on patient survival

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Abstract: To explore the application of afatinib combined with NP regimen in the treatment of stage IV non-small cell lung cancer and its effect on patient survival, the data of 100 patients with stage IV non-small cell lung cancer admitted to our hospital from February 2017 to February 2018 were retrospectively analyzed. They were equally divided into observation group and control group, with 50 in each group. The control group was treated with an NP regimen, and the observation group was treated with afatinib. The disease control rate (DCR) of the observation group was remarkably higher than that of the control group ($P<0.05$). The observation group witnessed a markedly higher clinical benefit rate relative to the control group ($P<0.05$). A remarkably longer median treatment failure time of the observation group was observed as compared to the control group ($P<0.001$). There was no statistical difference in the incidence of adverse reactions between the observation group and the control group ($P>0.05$). Afatinib combined with NP regimen treatment increases the clinical benefit rate of patients with stage IV non-small cell lung cancer, improves its short-term efficacy, and helps prolong the survival time of patients, with excellent safety profile.

Keywords: Afatinib, vinorelbine, cisplatin, non-small cell lung cancer.

INTRODUCTION

Lung cancer ranks as the first malignant tumor with the highest incidence and mortality rate in China. Roughly, 80.0%-85.0% are non-small cell lung cancer (Sasaki *et al*., 2021), including squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Its growth and division rate is rather slow and the metastasis and spreading are slow compared with small cell carcinoma, but patients are mostly in the middle and advanced stages when they are diagnosed, and the 5-year survival rate is not ideal (Divisi *et al*., 2021; Zhu *et al*., 2021). At present, clinical treatment is mainly based on the stages of non-small cell lung cancer. Surgical resection is the first choice for stage I, II and IIIA and comprehensive treatment is based on chemotherapy for stage IIIB and IV where surgical resection is not available (Kunimasa *et al*., 2021). Platinum drugs are the first-line chemotherapeutic drugs for the treatment of advanced non-small cell lung cancer. Previous study has shown that the NP regimen (vinorelbine + cisplatin) has a positive role (Jain *et al*., 2021; Pujol *et al*., 2021), with milder adverse reactions and a higher safety profile. However, clinical data show that the 1-year survival rate of stage IV patients with distant metastasis after chemotherapy is only 40.0%; and a small number of patients can live with tumors for several years, but their 5-year survival rate is still less than 2% (Okamoto *et al*., 2021), indicating that NP regimen, TP regimen (paclitaxel + cisplatin) and other conventional chemotherapy reach bottleneck. As a result, the use of other drugs to extend the survival of patients with stage IV emerges as the focus.

In addition to chemotherapy, targeted therapy also serves as a crucial measure to treat cancer. Targeted drugs for non-small cell lung cancer include endu, icotinib, gefitinib, afatinib, etc., among which afatinib is an EGFR inhibitor that targets the second-generation EGFR-TKI. The targeted EGFR gene is a common driver gene for non-small cell lung cancer and deletions, mutations or point mutations are prone to occur in non-small cell lung cancer (Kroemer and Kepp, 2021; Subramaniyan *et al*., 2021; Zhao *et al*., 2021). If there is no smoking habit, the EGFR mutation rate of non-small cell lung cancer is about 40%-60%, and the mutation rate of female non-smokers can exceed 70%, indicating that EGFR mutation plays a critical role in non-small cell lung cancer (Hill *et al*., 2021). Combining the actual situation of the patient, the combination of afatinib and NP regimen may contribute to prolonging the survival time of the patient. In this regard, this study was conducted based on it.

MATERIALS AND METHODS

Research design

This study is a retrospective study, and adopted a double-blind method. It was conducted in our hospital from February 2017 to February 2018.

Inclusion criteria and exclusion criteria

Inclusion criteria: The patient (1) was diagnosed with stage IV non-small cell lung cancer by cytopathology or histopathology(Pan *et al*., 2021); (2) was over 18 years old; (3) was expected to survive for more than 3 months;

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(4) had no central nervous system metastasis; (5) showed at least one CT measurable lesion; and (6) The NP regimen had been used in the past; (7) The NP regimen had been stopped for more than 6 months; (8) Liver, kidney function and blood routine were normal; (9) The patient met the treatment criteria for afatinib.

Exclusion criteria: The patient (1) Cannot communicate; (2) Withdrew from treatment midway; (3) Had other serious organic diseases; (4) Provided incomplete clinical data.

General patient information

A total of 100 patients were enrolled in this study and they were equally divided into observation group and control group according to the order of admission, with 50 patients in each group. There was no statistical difference in general data between the two groups (P>0.05), see table 1.

Moral considerations

This study complies with the principles of the *Declaration of Helsinki* (2013) (World Medical, 2013). After the patients were recruited, the research team explained the purpose, significance, content and confidentiality of the study to them, and asked them to sign an informed consent form.

Method

The control group was treated with NP regimen: vinorelbine (Hangzhou Minsheng Pharmaceutical Co., Ltd., approval no. H20051605) 25mg/m^2 was intravenously administered on the 1st and 8th days; cisplatin (Qilu Pharmaceutical Co., Ltd., approval no H37021356) 25mg/m^2 was intravenously administered on day 1, 2 and 3. Twenty-one days is taken as a cycle, for at least 2 cycles of treatment; the 24-month follow-up started when an intolerable side effect occurred or the patient requested to stop the treatment or 4 cycles of treatment were completed.

The observation group was treated with afatinib combined with an NP regimen. The NP regimen was administered in consistence with the control group. In addition, afatinib (Jiangsu Haosen Pharmaceutical Group Co., Ltd., approval no H20203229) was given at 1 tablet/d; the treatment cycle was the same as the NP program.

Observation indicators

(1) General information: The patient's gender, age, height, body mass, BMI, pathological type, medical history, living habits, marital status and education level were collected and compared.

(2) Short-term curative effect: After 4 weeks of treatment, the patient's tumor remission was assessed according to the WHO 2000 solid tumor curative effect evaluation standard (Terao *et al*., 2021). (1) Complete remission (CR): the lesion completely disappeared without new lesions, tumor markers returned to normal and maintained for more than 1 month; (2) Partial remission (PR): the sum of the maximum diameter of the target lesion reduced by more than 30% and was maintained for more than 1 month; (3) Stable disease (SD): the sum of the maximum diameter of the target lesion reduced by less than 30%, or increased by less than 20%; (4) Progressive disease (PD): the sum of the maximum diameter of the target lesion increased by 20% or more, or new lesions occurred. CR+PR=objective response rate (ORR), CR+PR+SD= disease control rate (DCR). The treatment effects of the two groups of patients were compared.

(3) Clinical benefit rate: the overall time of CR+PR+SD exceeding 6 months is regarded as a clinical benefit patient and the clinical benefit rate is calculated based on the follow-up results.

(4) Treatment failure time: the time for the patient to withdraw from the trial and the reasons may include efficacy, toxicity, safety, etc.; the treatment failure time of the two groups of patients was compared.

(5) The incidence of adverse reactions: the adverse reactions of patients during chemotherapy was recorded by rechecking blood routine, liver and kidney function, electrocardiogram and other data every week; the classification followed WHO's anti-cancer drug adverse reaction evaluation standards (Jing *et al*., 2021), the adverse reactions of patients after treatment were divided into 0-IV grade and the adverse reactions of the two groups of patients were recorded.

(6) Survival rate: the survival rate of patients who were followed up for 2 years was recorded.

(7) The relationship between afatinib treatment and the clinical characteristics of non-small cell lung cancer: the Cox proportional hazard model was used to analyze the impact of age, gender and tissue classification on the survival rate of patients treated with afatinib.

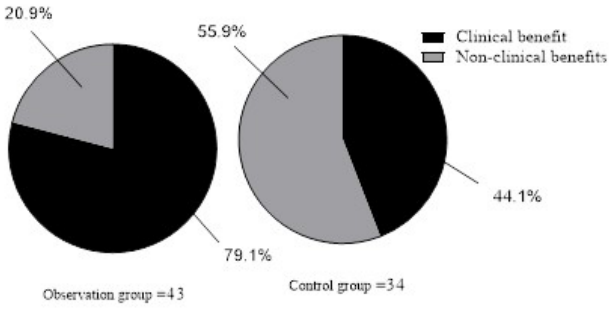
STATISTICAL ANALYSIS

The SPSS 20.0 software was used for data analysis and GraphPad Prism 7 (GraphPad Software, San Diego, USA) for graphic plotting. The count data and measurement data were expressed as X^2 test and *t*-test. *P*-value of 0.05 or lower was considered statistically significant. Cox proportional hazard model was employed for the analysis of multiple factors affecting survival.

RESULTS

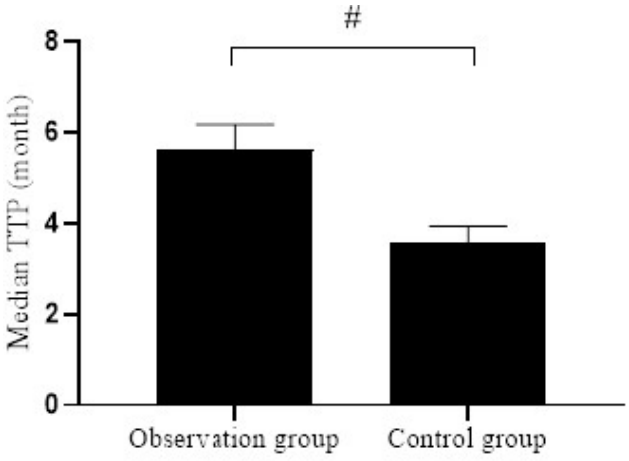
Comparison of general patient data

There was no statistical difference in general information between the two groups (P>0.05), see table 1.



Note: The left side of fig. 1 is the observation group, and the right side is the control group; The black areas in the figure are patients with clinical benefits and the gray areas are patients with non-clinical benefits.
The clinical benefit rate of the observation group was 79.1% (34/43) and that of the control group was 44.1% (15/34) (X2=10.024, P=0.002).

Fig. 1: Comparison of clinical benefit rate of patients [n(%)]



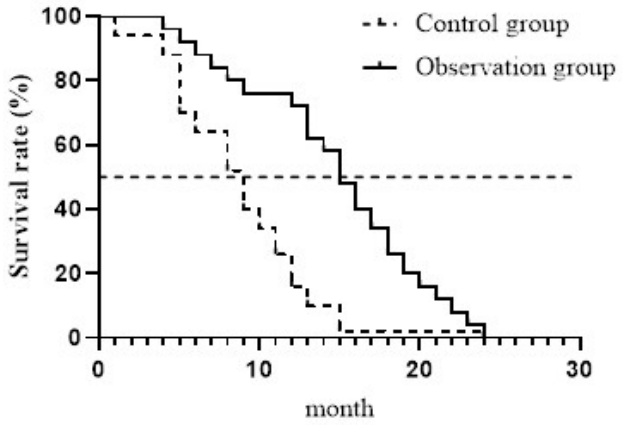
Note: The horizontal axis in Figure 2 is the observation group and the control group from left to right, and the vertical axis is the median treatment failure time (months); # means P<0.001.
The median treatment failure time in the observation group was significantly higher than that in the control group (5.64±0.54 vs 3.59±0.35, P<0.001).

Fig. 2: Comparison of patients' median treatment failure time (x±s) month

Comparison of patients' short-term efficacy
The DCR of the observation group was remarkably higher than that of the control group (P<0.05), see table 2.

Comparison of clinical benefit rate of patients
The observation group witnessed a markedly higher clinical benefit rate relative to the control group (P<0.05), as shown in fig. 1.

Comparison of patients' treatment failure time
A remarkably longer median treatment failure time of the observation group was observed as compared to the control group (P<0.001), as shown in fig. 2.



Note: In fig. 3, the horizontal axis is the month, and the vertical axis is the survival rate (%); the dotted line in the figure is the control group, and the solid line is the observation group.

Fig. 3: Comparison of patient survival rates

Comparison of the incidence of adverse reactions in patients
There was no statistical difference in the incidence of adverse reactions between the observation group and the control group (P>0.05), see table 3.

Comparison of patient survival rates
The observation group yielded a distinctively higher 2-year survival rate in comparison with the control group (P<0.05), as shown in fig. 3.

The relationship between afatinib treatment and clinical features of non-small cell lung cancer
Gender, age and tissue classification have no impact on the survival rate of patients with non-small cell lung cancer treated with afatinib, as shown in table 4.

DISCUSSION

As the malignant tumor with the highest incidence and fatality rate, the treatment of lung cancer has always been the focus of clinical research. Among lung cancers, non-small cell lung cancer accounts for as much as 80.0%, which can only be cured by surgery. However, most patients have entered the terminal stage of the disease when they are diagnosed, especially stage IV patients who have developed distant metastases, thus missing the opportunity for surgery (Evers *et al*., 2021; Li *et al*., 2021). For stage IV patients, chemotherapy and targeted therapy are the most important treatment measures, which are aimed at prolonging the patient's life span and reducing their pain perception. The current platinum-based chemotherapy regimen is the first-line regimen for the treatment of advanced non-small cell lung cancer. Patients who are effectively treated but progress after 6 months can continue to use the original regimen, but some patients have poor sensitivity to chemotherapy, or drug

resistance gradually develops in the course of treatment (Aggarwal *et al*., 2021; Hockenhull *et al*., 2021), leading to a somber chemotherapy outcome. A report in the United States pointed out that the overall response rate of platinum-based chemotherapy for patients with advanced non-small cell lung cancer in the United States was 20.0%; the median survival time of patients was (8.21±1.22) months, and the 1-year survival rate was below 35.0%, and the 2-year survival rate was less than 15.0% (Murat-Ringot *et al*., 2021), suggesting that chemotherapy for advanced non-small cell lung cancer has reached a plateau and the survival benefit of patients is limited.

To further improve the treatment effect of patients with advanced non-small cell lung cancer, a number of randomized clinical trials were conducted to evaluate the safety and effectiveness of molecularly targeted drugs combined with chemotherapy. It has been found that targeted drugs function in improving the survival of patients (Wang ZL *et al*., 2021). Afatinib, a first-line treatment for advanced non-small cell lung cancer, is a potent and irreversible dual inhibitor of EGFR and HER2 tyrosine kinase. Its mechanism of action is to continuously and selectively block ErbB family receptors. Scholar Saw Stephanie PL *et al*. stated that afatinib treatment compared with gefitinib can reduce the risk of lung cancer progression by 27.0% and the progression-free survival of patients will increase significantly over time (Saw *et al*., 2021), indicating that the irreversible ErbB family of blockers produce more superior long-term benefits. The results of this study showed that the disease control rate and clinical benefit rate of the observation group were significantly higher, the treatment failure time was longer and the patient's 2-year survival rate was better than those of the control group. It shows that the combination of the drug and the NP regimen does emanate a more ideal long-term benefit.

LUX-Lung 8test data show that afatinib compared with erlotinib considerably delays the disease progression of patients with lung squamous cell carcinoma and prolongs

Table 1: Comparison of general information of patients

	Observation group (n=50)	control group (n=50)	X^2/t	P
Gender			0.164	0.685
Male	28	30		
Female	22	20		
Age (year)				
Range	25-74	28-75		
Mean age	56.98±5.65	57.05±5.74	0.061	0.951
Average height(cm)	172.35±10.35	173.11±10.25	0.369	0.713
Average BMI(kg)	54.21±2.65	54.11±2.60	0.190	0.849
BMI(kg/m^2)	21.33±1.20	21.36±1.20	0.125	0.901
Pathological type				
Squamous cell carcinoma	18	20	0.170	0.680
Adenocarcinoma	24	25	0.040	0.841
Undifferentiated carcinoma	8	5	0.796	0.372
Medical history				
Diabetes	12	10	0.233	0.629
Hypertension	15	18	0.407	0.523
Hyperlipidemia	14	15	0.049	0.826
Marital status			0.060	0.806
Married	39	40		
Single	11	10		
living habit				
Smoking	35	36	0.049	0.826
Drinking	28	26	0.161	0.688
Educational background			0.040	0.841
High school and below	26	27		
University and above	24	23		

Table 2: Comparison of the overall efficacy of patients [n(%)]

	CR	PR	SD	PD	ORR	DCR
Observation group	1(2.0)	15(30.0)	27(54.0)	7(14.0)	16(32.0)	43(86.0)
control group	0(0.0)	10(20.0)	24(48.0)	16(32.0)	10(20.0)	34(68.0)
X^2	1.010	1.333	0.360	4.574	1.871	4.574
P	0.315	0.248	0.548	0.032	0.171	0.032

Table 3: Comparison of the incidence of adverse reactions in patients [n(%)]

	Observation group (n=50)	References group (n=50)	X^2	P
Leukopenia			0.271	0.603
0-α	40(80.0)	42(84.0)		
β–χ	10(20.0)	8(16.0)		
Reduced hemoglobin			1.191	0.275
0-α	40(80.0)	44(88.0)		
β–χ	10(20.0)	6(12.0)		
Nausea and vomiting			0.049	0.826
0-α	35(70.0)	36(72.0)		
β–χ	15(30.0)	14(28.0)		
Thrombocytopenia			0.233	0.629
0-α	38(76.0)	40(80.0)		
β–χ	12(24.0)	10(20.0)		
Impaired liver function			0.457	0.499
0-α	35(70.0)	38(76.0)		
β–χ	15(30.0)	12(24.0)		
Muscle ache			0.332	0.564
0-α	42(84.0)	44(88.0)		
β–χ	8(16.0)	6(12.0)		
Abnormal ECG			1.010	0.315
0-II	49(98.0)	50(100.0)		
III-IV	1(2.0)	0(0.0)		
Peripheral nerve toxicity			-	-
0-II	50(100.0)	50(100.0)		
III-IV	0(0.0)	0(0.0)		
diarrhea			0.122	0.727
0-II	45(90.0)	46(92.0)		
III-IV	5(10.0)	4(8.0)		

Table 4: The relationship between afatinib treatment and the clinical characteristics of non-small cell lung cancer

	B	SE	Wald	Df	Sig	Exp (B)	95% CI for Exp (B) Lower value	upper value
Age	0.412	0.318	1.685	1	0.210	1.512	0.810	2.811
Gender	0.198	0.548	0.123	1	0.735	1.216	0.420	3.568
Tissue type	0.354	0.465	0.435	1	0.561	1.368	0.564	3.426

their overall survival. Afatinib plays a prominent role in improving survival outcomes and is not affected by tumor EGFR mutation status, indicating that afatinib is a feasible treatment option (Wang X *et al*., 2021). In recent years, China has gradually relaxed the indications of afatinib, with which advanced non-small cell lung cancer that has progressed during or after chemotherapy with platinum drugs can be treated (Cheng *et al*., 2021; Fang *et al*., 2021). Additionally, the present study shows that gender, age and tissue classification exert no effect on the survival rate of patients with non-small cell lung cancer treated with afatinib, confirming the definite clinical value of afatinib. However, with the expansion of the application range of afatinib, reports of its adverse reactions have also been on a rise. Afatinib may cause diarrhea, skin rash, stomatitis and other adverse reactions, and its incidence and severity are higher than those of Iressa and Tarceva. This study showed that there was no statistical difference in the incidence of adverse reactions between the two groups and the possible adverse reactions when the drug is used in combination with the NP regimen still need to be further explored.

CONCLUSION

Collectively, afatinib combined with NP regimen treatment increases the clinical benefit rate of patients with stage IV non-small cell lung cancer, improves its short-term efficacy and helps prolong the survival time of patients, with a high safety profile, which merits widespread promotion.

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