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ORIGINAL ARTICLE

# Analysis of efficacy and prognosis of Osimertinib combined with docetaxel for non-small cell lung cancer

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## Summary

***Purpose:*** *To explore the therapeutic effects and prognosis of osimertinib combined with docetaxel for non-small cell lung cancer (NSCLC).*

***Methods:*** *A total of 94 patients with NSCLC diagnosed in hospitals of Changzhou were selected and randomly divided into two groups of 47 patients each. Patients in the control group took osimertinib tablets, while patients in the drug combination group were given intravenous docetaxel in addition to the oral administration of osimertinib. The therapeutic effects, inflammatory factors, toxic and side effects and factors affecting prognosis were analyzed in the two groups.*

***Results:*** *The overall response rate (RR) and disease control rate (DCR) in the drug combination group were 25.53% and 57.44%, respectively, which were higher than those in the control group. Before treatment, there were no obvious differences in terms of the levels of vascular endothelial growth factor (VEGF), matrix metallopeptidase-9 (MMP-9) and cytokeratin19 fragment antigen 21-1 (CYFRA21-1) between the two groups of patients. After treatment, the levels of the above indicators were lower in the drug combination group than in the control group. Patients in the two groups demonstrated significantly different degrees of side effects during treatment, including fatigue, thrombocytopenia and neutropenia. Smoking history, Karnofsky performance scale (KPS) score and TNM staging were important indicators affecting the prognosis of NSCLC patients. KPS score <70 and TNM stage IV were independent risk factors for the prognosis of NSCLC patients. After follow-up for 2 years, it was found that the survival rate was remarkably different between the two groups. The survival rate was notably higher in the drug combination group than in the control group.*

***Conclusions:*** *The therapeutic effect of osimertinib combined with docetaxel is better than that of osimertinib alone, but the toxic and side effects of combined use are significantly higher, suggesting that enteral administration should be conducted during the medication period. Patients with smoking history, advanced TNM stage and high KPS score tend to have a poor prognosis.*

***Key words:*** *NSCLC, osimertinib, docetaxel*

## Introduction

Lung cancer is a malignancy occurring on the bronchial mucosa [1]. At present, it has emerged as one of the diseases with extremely high morbidity and mortality rates worldwide, causing nearly 1.4 million deaths every year. Lung cancer can be divided into several types based on specific kinds of cancer cells, and non-small cell lung cancer (NSCLC) is a common type [2]. Epidemiological research results have demonstrated that in Asian countries, NSCLC is more prevalent than its counterparts, with the incidence rate accounting for more than 78% of the total incidence rate of lung cancers, which has become a challenge for the global healthcare community [3,4]. One study has point-

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ed out that NSCLC is caused by the mutation of the epidermal growth factor receptor (EGFR). Patients tend to show no obvious respiratory symptoms in the early stage, so most of them are diagnosed in stage III or IV, which are difficult to cure and have a poor prognosis [5]. Moreover, one study has revealed that the 5-year survival rate of patients with NSCLC is only 15%, hence it is vital to prolong the life cycle and improve the quality of life of patients with NSCLC and those with metastatic disease [6].

Osimertinib is a small molecule targeting EGFR with mono-anilino-pyrimidine as its mother nucleus [7]. John et al [8] pointed out that the oral administration of osimertinib in NSCLC patients can effectively inhibit the EGFR signaling pathway and lower its expression, indicating that osimertinib can effectively block the EGFR downstream signals and induce EGFR mutation to degrade cells [9]. Docetaxel, also known as taxotere, is a taxane antitumor drug. Docetaxel can enhance tubulin polymerization and inhibit its depolymerization to generate stable non-functional microtubule bundles, thus preventing the mitosis of tumor cells. Docetaxel is better than paclitaxel in terms of anti-tumor activity [10,11]. Therefore, this study explored the therapeutic effect and prognosis of osimertinib combined with docetaxel in NSCLC.

## Methods

*Subjects*

A total of 94 patients diagnosed with NSCLC according the standards for the diagnosis and treatment of primary lung cancer (2015) in China who were treated in 2017 with osimertinib alone or combined with docetaxel were selected as research subjects. According to treatment, the patients were divided into the control group and the drug combination group, each containing 47 cases. In the control group, there were 32 males and 15 females with an average age of 54.34 ± 15.67 years, 36 patients in stage II and III and 11 patients in stage IV, and 41 cases had a smoking history. In the drug combination group, there were 30 males and 17 females with an average age of 56.09 ± 14.12 years, 34 cases in stage II and III and 13 cases in stage IV. There were no statistical differences in general data between the two groups, as shown in Table 1.

*Inclusion criteria*

The inclusion criteria for this study were as follows: pathologically confirmed NSCLC, expected survival of more than 6 months, no cancer surgery, no radiotherapy or chemotherapy before admission, no contraindications to chemotherapy, and good treatment compliance. All patients met the relevant requirements of the Medical Ethics Committee of our hospital and signed informed consent forms.

*Administration method*

In the control group, patients with NSCLC received oral administration of 80 mg of osimertinib (AstraZeneca AB) once a day, one tablet at a time, for 3 weeks as a course of treatment. In addition to taking the same drug as those in the control group, the patients in the drug combination group were given 80 mg of docetaxel (Hubei Jusheng Technology co., Ltd., Hebei, China) by intravenous injection every 21 days. All patients underwent 4 courses of treatment.

*Karnofsky performance scale (KPS) score*

Patients in the two groups were observed and scored in terms of activity, disease condition and self-care. Scoring criteria: 100 points indicated good physical condition, >70 points indicated tolerance to the side effects of chemotherapy, and <60 points indicated inability to implement an antitumor therapy.

*Observation of various indicators*

Response evaluation criteria in solid tumors (RECIST)]: complete response (CR): complete remission of lesions, partial response (PR): partial remission of lesions, stable disease (SD): stable lesions, and progressive disease (PD): slight remission or occurrence of new lesions. Overall response rate (RR) = CR+PR/the number of people ×100. Disease control rate (DCR) = CR+PR+SD/the number of people ×100.

Changes in vascular endothelial growth factor (VEGF), matrix metallopeptidase-9 (MMP-9) and cytokeratin19 fragment antigen 21-1(CYFRA21-1) were observed in the two groups of patients. A total of 2 mL venous blood was drawn from each patient in the two groups before and after treatment. The changes in the indicators mentioned above were detected by enzyme-linked immunosorbent assay (ELISA).

*Side effects*

Patients in the two groups were monitored for side effects during treatment, including fatigue, gastrointesti-

**Table 1.** Basic information

| *Group* | *Sample size (n)* | *Male (n)* | *Female (n)* | *Average age (years) mean±SD* | *Stage II-III (n)* | *Stage IV (n)* |
|---|---|---|---|---|---|---|
| Control group | 47 | 32 | 15 | 54.34 ± 15.67 | 36 | 11 |
| Drug combination group | 47 | 30 | 17 | 56.09 ± 14.12 | 34 | 13 |
| $x^2$ | | 0.065 | 0.125 | 0.028 | 0.057 | 0.167 |
| p | | 0.798 | 0.723 | 0.867 | 0.811 | 0.682 |

nal reactions and proteinuria. The evaluation was carried out in strict accordance with CTCAE 4.0.

*Follow-up*

All patient data were recorded in detail. Univariate regression analysis was performed on the indicators affecting the patient prognosis. Outpatient visits were conducted every 3 months after treatment. The follow-up investigations were asked by phone.

*Statistics*

SPSS 18.0 (SPSS, Chicago, IL, USA) software was used for analyses. The correlation of clinical efficacy, factor expression, side effects and factors influencing prognosis in the two groups of patients was examined by t-test, and the enumeration data were verified by $x^2$ test. Survival curves were plotted using Kaplan-Meier method and were compared with log-rank test. P<0.05 was considered to represent a statistically significant difference.

## Results

*Therapeutic effects in two groups of patients*

The RR and DCR of patients in the drug combination group were 25.53% and 57.44%, while those of the patients in the control group were 10.63% and 36.17%, respectively. The differences between the data were statistically significant (p<0.05), as shown in Table 2.

*Various indicators before and after treatment*

There were no remarkable differences in VEGF, MMP-9 and CYFRA21-1 between the two groups before treatment (p<0.05). After treatment, the levels of these indicators were lower in the drug combination group than in the control group (p<0.05), as shown in Table 3.

**Table 2.** Therapeutic effects in the two groups of patients

| *Group* | *n* | *CR* *n (%)* | *PR* *n (%)* | *SD* *n (%)* | *PD* *n (%)* | *RR* *n (%)* | *DCR* *n (%)* |
|---|---|---|---|---|---|---|---|
| Control group | 47 | 0 (0.00) | 5 (14.89) | 12 (21.27) | 30 (63.83) | 5 (10.63) | 17 (36.17) |
| Drug combination group | 47 | 0 (0.00) | 12 (25.53) | 15 (31.91) | 20 (42.55) | 12 (25.53) | 27 (57.44) |
| $x^2$ | | | | | | 6.140 | 4.437 |
| p | | | | | | 0.013 | 0.035 |

**Table 3.** Various indicators before and after treatment (mean±SD)

| *Group* | *n* | *VEGF (ng/L)* | | *MMP-9 (μg/L)* | | *CYFRA21-1 (μg/L)* | |
|---|---|---|---|---|---|---|---|
| | | *Before treatment* | *After treatment* | *Before treatment* | *After treatment* | *Before treatment* | *After treatment* |
| Control group | 47 | 750.42±68.09 | 495.67±45.34[a] | 1509.34±256.02 | 1248.04±112.41[a] | 7.78±1.45 | 5.56±0.67[a] |
| Drug combination group | 47 | 755.21±69.12 | 289.45±34.19[a] | 1511.56±260.48 | 873.29±67.98[a] | 7.93±1.48 | 2.19±0.32[a] |
| $x^2$ | | 0.338 | 24.90 | 0.041 | 18.46 | 0.496 | 31.12 |
| p | | 0.736 | <0.0001 | 0.966 | <0.0001 | 0.620 | <0.0001 |

[a]p<0.05 *vs.* before treatment in each group

**Table 4.** Analysis of side effects (n)

| *Side effects* | *Control group* | | *Drug combination group* | | $x^2$ | *p* |
|---|---|---|---|---|---|---|
| | *Level 1-2* | *Level 3-4* | *Level 1-2* | *Level 3-4* | | |
| Neutropenia | 3 | 7 | 12 | 14 | 7.111 | 0.007 |
| Thrombocytopenia | 5 | 1 | 10 | 6 | 4.545 | 0.032 |
| Anemia | 9 | 0 | 12 | 0 | 0.429 | 0.512 |
| Gastrointestinal reaction | 17 | 3 | 19 | 5 | 0.364 | 0.546 |
| Fatigue | 6 | 1 | 14 | 3 | 4.167 | 0.041 |
| Proteinuria | 0 | 0 | 2 | 0 | 2.000 | 0.157 |
| Hemorrhage | 1 | 0 | 2 | 0 | 0.333 | 0.563 |
| Hypertension | 0 | 0 | 1 | 0 | 1.000 | 0.317 |

**Table 5.** Univariate analysis of prognostic and survival factors in NSCLC patients

| *Basic item* | *n* | *2-year survival rate (%)* | $x^2$ | *p* |
|---|---|---|---|---|
| Age, years | | | 0.028 | 0.867 |
| ≥60 | 34 | 25.91 | | |
| <60 | 60 | 27.12 | | |
| Gender | | | 0.025 | 0.874 |
| Male | 63 | 26.13 | | |
| Female | 31 | 27.28 | | |
| Smoking history | | | 4.863 | 0.027 |
| Yes | 66 | 18.94 | | |
| No | 28 | 35.16 | | |
| KPS score | | | 4.410 | 0.035 |
| ≥70 | 41 | 37.23 | | |
| <70 | 53 | 21.18 | | |
| Treatment methods | | | 5.213 | 0.013 |
| Osimertinib | 47 | 33.21 | | |
| Combined therapy | 47 | 73.17 | | |
| Treatment courses | | | 0.088 | 0.956 |
| <3 | 20 | 25.09 | | |
| 3-6 | 43 | 26.13 | | |
| >6 | 21 | 27.24 | | |
| TNM staging | | | 4.851 | 0.027 |
| II-III | 54 | 31.89 | | |
| IV | 40 | 16.56 | | |

KPS: Karnofsky performance status

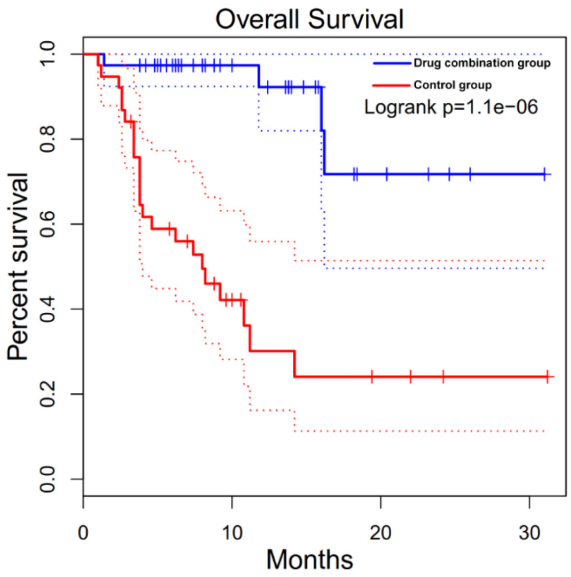


**Figure 1.** Overall survival curves in the two groups of patients.

*Analysis of side effects*

Patients in the two groups showed different degrees of side effects during treatment. The incidence rates of fatigue, thrombocytopenia and neutropenia were significantly higher in the drug combination group than in the control group. The differences in data comparisons were statistically significant ($p<0.05$), and there were no other remarkable changes, as shown in Table 4.

*Univariate analysis of prognostic and survival factors in NSCLC patients*

The log-rank test proved that smoking history, KPS score and TNM staging were important indicators affecting the prognosis and survival of NSCLC patients ($p<0.05$), as shown in Table 5.

*Analysis of survival curves in two groups of patients*

After follow-up for 2 years, it was found that the survival rate was significantly higher in in the drug combination group compared with the control group, as shown in Figure 1.

## Discussion

Lung cancer mainly occurs in the epithelium of the bronchial mucosa. According to the different types of cancer cells, it can be divided into NSCLC and other types [12]. Several studies have mentioned that the incidence rate of NSCLC is 80%. The incidence of lung cancer is very high in China, especially in males, with nearly 150,000 deaths every year causing great physical and mental harm

[13,14]. Similar to most cancers, NSCLC is initially occult, so patients tend to be in an advanced stage or have metastasis at the time of diagnosis which worsens prognosis and reduces survival. Therefore, it is essential to prolong patient life and improve prognosis [15].

According to the results of this study, RR and DCR after treatment were 25.53% and 57.44% in the drug combination group, which were significantly higher than the 10.63% and 36.17% registered in the control group ($p<0.05$). Before treatment, there were no significant changes in inflammatory factors like VEGF, MMP-9 and CYFRA21-1 in NSCLC patients in the two groups ($p>0.05$). After treatment, the expression of inflammatory factor activity was inhibited in the two groups, and the inflammatory factor activity was lower in the drug combination group than in the control group ($p<0.05$). As a third-generation EGFR inhibitor [16], osimertinib can inhibit EGFR sensitivity and secondary effects, as it is the most common clinical anti-EGFR sensitivity drug with excellent therapeutic effect. Docetaxel is a semi-synthetic paclitaxel anticancer drug, whose mechanism of action is to strengthen tubulin polymerization and inhibit tubulin depolymerization [17,18]. Some studies have put forward that osimertinib combined with docetaxel can lead to better outcome in the treatment of NSCLC. A previous study [19] used oseltamivir alone in 24 of 48 patients with NSCLC, while the other 24 patients were treated with osimertinib combined with docetaxel. The results showed that the combined use of drugs can significantly reduce the levels of VEGF, MMP-9 and CYFRA21-1 in serum compared with the levels before treatment [20]. Many studies have pointed out that MMP-9 and VEGF are essential products for tumor cell proliferation and differentiation. The level of VEGF is abnormally increased in tumor patients, but quite low in healthy individuals, which indicates that the active expression of VEGF accelerates the growth and differentiation of tumor cells. MMP-9 exists in various cancer cells and is often chosen to reflect the metastasis of tumor cells. CYFRA21-1 is an essential product for cell apoptosis and necrosis in alveoli, increased levels being able to deteriorate the condition of NSCLC patients and affect their prognoses.

According to the results of this study, patients in the two groups had different degrees of side effects during treatment, among which there were differences in fatigue, thrombocytopenia and neutropenia ($p<0.05$). Long smoking history, KPS score and TNM staging exerted an important influence on the prognosis of NSCLC patients ($p<0.05$). After follow-up for 2 years, it was found that the survival rate was significantly higher in the drug combination group than in the control group. NSCLC is specific, but the quality of life and prognosis vary according to individual differences. The combined use of osimertinib and docetaxel tends to make adverse reactions more common. Patients may suffer from an obvious reduction of neutrophils, platelet dysfunction, and various degrees of fatigue and gastrointestinal reactions. Hence, it becomes vital to provide appropriate enteral nutrition during treatment [21,22]. TNM stage IV patients had decreased survival, while the survival rate of patients with stage II and III was significantly improved, which suggests that early treatment can effectively prolong the patient life.

## Conclusions

To sum up, the clinical effect of osimertinib combined with docetaxel for cancer treatment is distinctly better than that of osimertinib alone, but the toxic and side effects of combined use are clearly higher, suggesting that appropriate enteral administration should be conducted during the medication period. Patients with advanced TNM stage and high KPS score tend to have a poor prognosis.

## Conflict of interests

The authors declare no conflict of interests.

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