Clinical effect of anlotinib in combination with docetaxel in treating advanced non-small cell lung cancer

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This study aimed to explore the clinical performance of anlotinib in combination with docetaxel in treating advanced non-small cell lung cancer (NSCLC). One hundred advanced NSCLC patients admitted to our hospital from January 2019 to December 2022 were retrospectively chosen to be the study objects, and separated into observation group (OG, n=50) and control group (CG, n=50) based on the different drugs used. The CG was given docetaxel injection. The OG was treated with anlotinib hydrochloride capsule combined with docetaxel injection. The clinical effective rate, levels of serum tumor markers, quality of life and occurrence of adverse reactions in both groups were compared. The total clinical effective rate in the OG presented elevated relative to the CG (P<0.01). After treatment, CEA, CA125, SCC and CYFRA21-1 levels in both groups were decreased, and those in the OG presented lower relative to the CG (P<0.05). After treatment, KPS score in both groups was increased and that in the OG presented higher relative to the CG (P<0.05). No difference was seen in the occurrence of adverse reactions between 2 groups (P=0.35). In treating advanced NSCLC patients, anlotinib combined with docetaxel can promote efficacy to a certain extent, effectively regulate the level of serum tumor markers, promote the quality of life of patients, and will not significantly affect clinical safety.

Keywords: Advanced non-small cell lung cancer, Anlotinib, Docetaxel, Chemotherapy.

1. Introduction

Lung cancer belongs to the most common clinical malignant tumor, and non-small cell lung cancer (NSCLC) takes up 80% to 85% of lung cancer [1]. Because patients with early NSCLC often have no typical symptoms, many patients have entered the middle and late stage of the disease at the time of diagnosis, missed the opportunity for surgical treatment, and even some tumors metastasized, and can only alleviate symptoms through radiotherapy and chemotherapy to prolong survival [2]. Platinum-containing double-drug chemotherapy is the current first-line chemotherapy regimen for the clinical treatment of advanced NSCLC patients, which can relieve the symptoms of patients to a certain extent [3]. However, some patients have poor chemotherapy effects or even chemotherapy failure due to drug resistance during treatment, so second-line or third-line chemotherapy regimen should be used for treatment [4].

Docetaxel is a plant chemotherapeutic agent that can accelerate the apoptosis process of cancer cells by inhibiting microtubule depolymerization and normal recombination [5], and docetaxel alone is currently the second-line standard chemotherapy regimen for the clinical treatment of advanced NSCLC [6]. Since long-term application of docetaxel can easily result in drug resistance in patients, and then adversely affect the subsequent tumor inhibition effect, it is necessary to combine it with less dose-dependent drugs to improve the tumor inhibition effect [7]. Hence, it is essential to explore a safe as well as efficient chemotherapy regimen for advanced NSCLC patients who have failed second-line chemotherapy.

Anlotinib is a novel multi-target tyrosine kinase inhibitor independently developed in China, which has anti-tumor angiogenesis effect and low incidence of adverse reactions [8]. Relevant studies have reported that anlotinib can demonstrate good efficacy in various malignant tumors such as NSCLC and cervical cancer [9, 10].

Therefore, our study explored the clinical performance of anlotinib combined with docetaxel in treating advanced NSCLC, aiming to provide reference for patients to develop multi-line chemotherapy regimens.

2. Materials and Methods

2.1. General data

One hundred patients with advanced NSCLC admitted to our hospital from January 2019 to December 2022 were retrospectively chosen to be the study objects, and separated into observation group (OG, n=50) and control group...
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2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Met the diagnostic criteria of NSCLC; (2) Estimated survival time >3 months; (3) TNM stages ranged from IIIb to IV; (4) Could tolerate chemotherapy; (5) Good compliance; (6) Progression of the disease after first-line chemotherapy; (6) All patients sign informed consent forms.

Exclusion criteria: (1) There are other types of malignant tumors; (2) Acute blood disease; (3) Persons with conscious or mental disorders; (4) Allergic reactions to investigational drugs; (5) Patients who could not insist on completing chemotherapy due to serious adverse reactions.

2.3. Methods

The CG was given docetaxel injection (Qilu Pharmaceutical Co., LTD., specification: 4 ml vs. 80 mg) 75 mg/m² mixed with 250 ml normal saline for treatment, 21 days for 1 treatment cycle. The drug was stopped for 20 days after intravenous infusion on day 1 of each treatment cycle.

The OG was treated with anlotinib hydrochloride capsule (Zhengda Tianqing Pharmaceutical Group Co., LTD., specification: 12 mg) combined with docetaxel injection. Oral antirotinib hydrochloride capsule 12 mg once a day. After 14 days of treatment, the drug was stopped for 7 days, and 21 days was 1 cycle. Both groups were treated for 4 cycles.

2.4. Observation index and evaluation criteria

(1) Clinical effective rate: On the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [11], complete remission (CR) meant the target lesion disappeared completely after treatment. Partial response (PR) meant the target lesion volume decreased by >50% after treatment. Stable disease (SD) meant the volume of target lesion decreased by less than 50% after treatment. Progressive disease (PD) meant the target lesion volume increased by >25% or new lesions appeared after treatment. Total clinical effective rate = (CR+PR)/total cases ×100%.

(2) Serum tumor markers: Carcinoembryonic antigen (CEA), glycoprotein antigen 125 (CA125), squamous cell carcinoma antigen (SCC) as well as Cytokeratin fragment antigen 21-1 (CYFRA21-1) were detected by ELISA.

(3) Quality of life: The Karnofsky Performance Status (KPS) was compared between 2 groups. This scale comprehensively evaluated the quality of life of tumor patients from the dimensions of self-care ability and symptom severity. The full score was 100, and the higher the score was, the better the quality of life was.

(4) The occurrence of hematotoxic reactions (platelet count decrease, white blood cell count decrease, as well as granulocyte count decrease) and non-hematotoxic reactions (hypertension, fatigue and proteinuria) were compared between the two groups.

2.5. Statistical analysis

The data were processed by SPSS 23.0 statistical software. Measurement data were exhibited as (x±s) and t-test was adopted for comparison. The statistical data were represented by [n (%)] and χ² test was performed for comparison. P<0.05 meant the difference was statistically significant.

3. Results

3.1. Clinical effects in both groups

Table 2 displayed that the total clinical effective rate in the OG was 52.22%, presented elevated relative to that of 24.00% in the CG (P<0.01).

3.2. Serum tumor markers in both groups

Figure 1 displayed no difference in levels of serum tumor markers in both groups.

Table 1. General data of patients in both groups.

<table>
<thead>
<tr>
<th>Index</th>
<th>Control group (n=50)</th>
<th>Observation group (n=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>25/25</td>
<td>26/24</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>48.42±5.73</td>
<td>48.36±5.70</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Type of NSCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>30</td>
<td>29</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>20</td>
<td>21</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>19</td>
<td>20</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Stage IV</td>
<td>31</td>
<td>30</td>
<td></td>
</tr>
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Table 2. Clinical effects in both groups [n (%)].

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PR</th>
<th>Total clinical effective rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>2</td>
<td>10</td>
<td>25</td>
<td>13</td>
<td>12 (24.00%)</td>
</tr>
<tr>
<td>Observation group</td>
<td>50</td>
<td>5</td>
<td>21</td>
<td>21</td>
<td>3</td>
<td>26 (52.22%)</td>
</tr>
<tr>
<td>χ²</td>
<td>8.319</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Serum tumor markers in both groups. *P<0.05, compared with before therapy. **P<0.05, compared with CG.
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3.3. Quality of life in both groups

Figure 2 displayed no difference in KPS score between 2 groups previous to therapy (P>0.05). After treatment, KPS score in both groups was elevated in both groups and that in the OG presented higher relative to the CG (P<0.05).

3.4. Occurrence of adverse reactions in both groups

Table 3 revealed no difference in the occurrence of adverse reactions between 2 groups (P=0.35).

4. Discussion

Since surgery cannot play a good role in treating advanced NSCLC, chemotherapy has become the current clinical treatment of this disease, which is of great importance in controlling the proliferation and metastasis of tumor cells as well as prolonging the survival of patients [12]. For the past few years, with the gradual deepening of clinical research on the treatment of advanced NSCLC, it has been found that more chemotherapy drugs can be used for this disease [13]. However, affected by many adverse factors, some patients cannot achieve the expected effect after first-line chemotherapy, and some patients also have problems such as short duration of efficacy and high drug toxicity when receiving second-line chemotherapy [14]. Therefore, the safe and efficient multi-line chemotherapy regimen for patients with advanced NSCLC has become a major direction of clinical research.

Docetaxel is a novel anti-microtubule drug, belonging to semi-synthetic derivatives, which can control the synthesis of tumor DNA, RNA and protein, enhance the assembly of microtubule dimers into microtubules on the basis of acting on microtubules, disturb the process of depolymerization, as well as maintain stability [15]. At present, many clinical reports have pointed out that docetaxel is an effective supportive chemotherapy drug for a variety of advanced malignant tumors and has a certain prolonging effect on the survival of patients [16]. However, it has also been reported that docetaxel alone has limited remission effect on patients with advanced malignant tumors, and continuous use of docetaxel has obvious side effects, and some patients may suffer from interruption or failure of chemotherapy due to their inability to tolerate chemotherapy [17].

As a targeted anti-angiogenesis drug, anlotinib can strengthen the inhibition of enzymes related to tumor cell proliferation, thus blocking downstream signal transduction along with repressing tumor growth [18]. Anlotinib is well absorbed orally, can promote the overall therapeutic effect, and is widely applied in the therapy of NSCLC, gastric cancer along with other tumor diseases [19, 20].

In our study, the outcomes revealed that after therapy, the total clinical effective rate in the OG was 52.22%, presented elevated relative to that of 24.00% in the CG, and CEA, CA125, SCC as well as CYFRA21-1 levels in the OG presented lower relative to the CG, suggesting that this combination chemotherapy regimen could improve the chemotherapy effect and inhibit the expression of serum tumor markers in treating advanced NSCLC to a certain extent. Consistently, Ji et al. have indicated that the total effective rate of anlotinib in combination with docetaxel in treating lung cancer is 57.14%, and can improve the long-term survival rate [21]. Moreover, a previous study has proved that the serum levels of tumor markers including VEGF, CEA, as well as SCC-AG in the anlotinib in combination with immune checkpoint inhibitors group present lower relative to the immune checkpoint inhibitors group alone [22].

Besides, our study indicated that after treatment, KPS score in the OG presented elevated relative to the CG, implying that anlotinib combined with docetaxel could promote the quality of life of advanced NSCLC patients. At the same time, no difference was seen in the occurrence of adverse reactions between 2 groups, confirming that anlotinib in combination with docetaxel in treating advanced NSCLC has no significant impact on clinical safety compared with docetaxel alone. In line with our finding, it has been reported that anlotinib in combination with docetaxel has been reported to show good efficacy and manageable toxicity in second-line therapy of metastatic osteosarcoma.

Table 3. Occurrence of adverse reactions in both groups [n (%)].

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>Platelet count decrease</th>
<th>White blood cell count decrease</th>
<th>Granulocyte count decrease</th>
<th>Hypertension</th>
<th>Fatigue</th>
<th>Proteinuria</th>
<th>Total incidence rate</th>
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</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>10 (20.00%)</td>
</tr>
<tr>
<td>Observation group</td>
<td>50</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>14 (28.00%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.877</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
</tbody>
</table>

**Fig. 2.** Quality of life in both groups. *P<0.05, compared with before therapy.  †P<0.05, compared with CG.
compared to docetaxel [23]. Additionally, Si et al. have proposed that anlotinib can enhance the quality of life compared to placebo in advanced NSCLC patients who have accepted more than two chemotherapy treatments [24-27].

5. Conclusion
In conclusion, in treating advanced NSCLC patients, anlotinib combined with docetaxel can promote efficacy to a certain extent, effectively regulate the level of serum tumor markers, promote the quality of life of patients, and will not significantly affect clinical safety.

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Conflict of interests
The author has no conflicts with any step of the article preparation.

Consent for publications
The author read and approved the final manuscript for publication.

Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions
WG conducted the experiments and wrote the paper; FW, LY and CL analyzed and organized the data; SW conceived, designed the study and revised the manuscript.

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None.

References
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