Efficacy and Adverse Reactions of Carboplatin, Nab-Paclitaxel Regimen Combined with Atezolizumab in the Treatment of Non-Small Cell Lung Cancer

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We attempt to study the efficacy and adverse reactions of carboplatin, nab-paclitaxel regimen combined with atezolizumab in non-small cell lung cancer treatment. We randomly selected 120 non-small cell lung cancer patients who received therapy in our hospital from January 2019 to December 2021 and divided them into two groups, 60 cases respectively. Treated control group with carboplatin and paclitaxel combined with pembrolizumab, while observation group with carboplatin and albumin paclitaxel combined with pembrolizumab. Compared both groups on the efficacy, incidence of adverse reactions, levels of peripheral blood lymphocyte subsets and serum tumor markers. After treatment, observation group possessed higher objective remission rate and disease control rate than control group (p<0.05); observation group had lower adverse reactions rate during the treatment period than control group (p<0.05); observation group had higher cluster of differentiation 3+, cluster of differentiation 4+ and cluster of differentiation 8+ values than control group, but it possessed lower cluster of differentiation 8+ values than control group (p<0.05). Observation group had lower cytokeratin 19 fragment antigen 21-L, squamous cell carcinoma antigen, carbohydrate antigen 125 and carcinoembryonic antigen levels than control group (p<0.05). Carboplatin, nab-paclitaxel regimen combined with atezolizumab in treating non-small cell lung cancer patients can effectively alleviate and control their disease, reduce the risk of adverse reactions during the treatment process and improve the body's immune function, which is worthy of promotion.

Key words: Carboplatin, nab-paclitaxel, atezolizumab, non-small cell lung cancer, efficacy, adverse reactions, peripheral blood lymphocyte

Non-Small Cell Lung Cancer (NSCLC) is one type lung cancer with higher incidence. Its occurrence and development are related to the immunity, innate immunity and adaptive immunity of host cells[1]. Currently, the main methods for NSCLC treatment are surgery, radiotherapy and chemotherapy. Among them, carboplatin is a commonly used first-line chemotherapy drug. It has been reported that T lymphocyte-dominated cellular immunity has some effects on the antitumor immune response; therefore, carboplatin combined with immunotherapy is often used to treat NSCLC patients[2]. Atezolizumab is a representative drug for immunotherapy, it is the lead drug approved by the United States (U.S). Food and Drug Administration (FDA) for advanced metastatic NSCLC treatment[3]. Paclitaxel is a natural anti-cancer drug, which is widely used in treating various cancers in clinic, but its toxic and side effects are relatively large. With the continuous advancement of medical technology, physicians have improved paclitaxel to make albumin-bound paclitaxel, it is a semi-synthetic paclitaxel special targeted preparation, and it has obvious effect and good safety in solid tumors treatment[4]. We attempt to study the clinical effect of carboplatin, nab-paclitaxel regimen combined with atezolizumab in NSCLC treatment.

MATERIALS AND METHODS

General data:
The study randomly selected 120 NSCLC patients under-treated in our hospital from January 2019 to December 2021 and divided them into two groups, 60 cases respectively. Control group has 38 males and 22 females included, ages were from 59 y to 81 y old, average were about (71.62±5.21) y old; pathological type have 25 cases adenocarcinoma, 17 cases squamous cell carcinoma, 9 cases large cell carcinoma and 9 cases sarcomatoid carcinoma. Observation group has 37 males and 23 females included, ages were from 60 y to 81 y old, average were about (71.72±5.33) y old; pathological type have 25 cases adenocarcinoma, 17 cases squamous cell carcinoma, 10 cases large cell carcinoma, 6 cases sarcomatoid carcinoma. After
comparison, gender, age and pathological type of both groups had no obvious difference (p>0.05). This study has gotten approval from the ethics committee of our hospital, ethics number 20181221.

Inclusion criteria and exclusion criteria:

Inclusion criteria: After pathological examination, it was found to be consistent with the diagnostic criteria for NSCLC in the ‘Chinese expert consensus on antiangiogenic drugs for advanced NSCLC’ (2020 edition)[5]; estimated lifetime >6 mo; those who did not receive any anti-tumor treatment before admission; neutrophil ≥1.5×10⁹/l, hemoglobin ≥100 g/l, platelet ≥100×10⁹/l, creatinine clearance rate ≥50 ml/min; those who have understood the purpose, significance and specific operation methods of this research and signed the consent form.

Exclusion criteria: Small cell lung cancer; abnormal coagulation function; patients are allergic to the drugs used in this study; combining immune system and blood system diseases; patients who cannot receive radiotherapy and chemotherapy and, patients with mental disorders and language barriers.

Drugs:

Dexamethasone (manufacturer: Sancai Shiqi Pharmaceutical Co., Ltd, national medicine permission number H44024276, size 0.75 mg); diphenhydramine (manufacturer: Southwest Pharmaceutical Co., Ltd, national medicine permission number H50020188, size 25 mg); cimetidine (manufacturer: Hainan Pharmaceutical Factory Co., Ltd, national medicine permission number H46020549, size 2 ml:0.2 g); paclitaxel (manufacturer: Jiangsu Aosaikang Pharmaceutical Co., Ltd, national medicine permission number H20083849, size 25 ml:150 mg); atezolizumab injection (manufacturer: Merck Sharp and Dohme (MSD) Ireland, Registration Certificate No S20180019, size 100 mg:4 ml/piece); carboplatin (manufacturer: Made by Bristol-Myers Squibb, Italy, Registration Certificate No H20110231, size 150 mg:15 ml/piece) and albumin paclitaxel (manufacturer: Abraxis Bio Science, USA, Registration Certificate No H20130650, size 100 mg).

Method:

Control group: Adopted carboplatin, paclitaxel combined with atezolizumab treatment, the medication method is as follows 12 h, 6 h before paclitaxel, took 3 mg of dexamethasone orally, injected 20 mg of diphenhydramine intramuscularly to the patient 30 min before paclitaxel, pretreatment with 300 mg cimetidine intravenously. Injected 175 mg/m² of paclitaxel into the patient intravenously for 3 h to 4 h. Atezolizumab injection was administered by intravenous drip every 3 w, 200 mg each time; carboplatin was administered intravenously according to Area Under the Curve (AUC)=5 mg/(ml/min). Took 3 w as a treatment cycle, injected the above drugs on the 1 d of each treatment cycle and evaluated the effect after continuous treatment for 2 cycles.

Observation group: Treatment with carboplatin, nab-paclitaxel regimen combined with atezolizumab, took the same usage and dosage of carboplatin and atezolizumab as control group, took 3 w as a treatment cycle, diluted 130 mg/m² albumin-paclitaxel with 100 ml normal saline and instilled it into the patient on the 1⁰ and 8⁰ d of each treatment cycle, 30 min each time and evaluated the effect after 2 cycles of continuous treatment. During treatment, if the patient had adverse reactions related to carboplatin and atezolizumab, the dose could be appropriately reduced in the next cycle.

Observation indicators:

Curative effect: After 2 cycles of treatment, evaluated the short-term efficacy of the patients. Complete disappearance of all lesions on imaging examination, it means complete remission; the sum of lesion diameters is smaller than the baseline and the reduction is ≥30 %, it means partial remission; the sum of lesion diameters tends to shrink, but it did not meet complete remission criteria, or an increase in the sum of diameters but not meeting the criteria for disease progression, it means stable disease; if the sum of lesion diameters has increased, the increase rate is ≥20 % or new lesions have appeared, it means disease progression[6].

Objective response rate=(Complete remission+partial remission)/cases×100 %

Disease control rate=(Complete remission+partial remission+stable disease)/cases×100 %.

Incidence of adverse reactions: Common adverse reactions are neutropenia, thrombocytopenia, anemia, thyroid dysfunction, liver or kidney function damage, etc. Calculate the incidence of adverse reactions in both groups.

Peripheral blood lymphocyte subset levels: Collected 2 ml of patient’s venous blood before and after treatment, after anticoagulation, adopted FACSCanto II automated flow cytometer produced by BD Company in the U.S to detect lymphocyte subsets levels in peripheral blood, including Cluster of Differentiation (CD) 3⁺, CD4⁺, CD8⁺ and CD4⁺/CD8⁺.
Serum tumor marker levels: Collected 5 ml of patient’s fasting venous blood before and after treatment, centrifugation at 3000 r/min for 10 min, detected serum tumor marker levels by Enzyme-Linked Immunosorbent Assay (ELISA) after separation of serum, including Cytokeratin 19 Fragment Antigen 21-1 (CYFRA21-1), Squamous Cell Carcinoma antigen (SCC-Ag), Carbohydrate Antigen 125 (CA125) and Carcinoembryonic Antigen (CEA).

Statistical methods:
Adopted Statistical Package for Social Sciences (SPSS) 20.0 software to process the data. Used $\bar{x} \pm s$ to represent measurement data that conform to a normal distribution and tested by $t$; used percentage (%) to express enumeration data, tested by Chi-square ($\chi^2$), $p<0.05$ was considered to possess statistically significant difference.

RESULTS AND DISCUSSION

Table 1 shows observation group possessed higher objective remission rate, disease control rate than control group ($p<0.05$). Table 2 shows observation group possessed lower adverse reaction rate than control group ($p<0.05$).

Table 3 shows that, before treatment, both groups had no significant difference in peripheral blood lymphocyte subsets levels ($p>0.05$); after treatment, compared with the same group before and after treatment, CD3+, CD4+, CD4+/CD8+ values of both groups after treatment were higher than before treatment, but CD8+ values was lower than before treatment ($p<0.05$), observation group possessed higher CD3+, CD4+ and CD4+/CD8+ values than control group, but it possessed lower CD8+ values than control group ($p<0.05$).

Table 4 shows that, before treatment, both groups had no significant difference in serum tumor marker levels ($p>0.05$); after treatment, compared with the same group before and after treatment, CYFRA21-1, SCC-Ag, CA125 and CEA values of both groups after treatment were lower than before treatment ($p<0.05$), but after treatment, the above indexes of observation group were lower than control group ($p<0.05$).

### TABLE 1: COMPARISON OF CLINICAL EFFICACY BETWEEN BOTH GROUPS (n, %)

<table>
<thead>
<tr>
<th>Group</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Stable disease</th>
<th>Disease progression</th>
<th>Objective remission rate</th>
<th>Disease control rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n=60)</td>
<td>2 (3.33)</td>
<td>19 (31.67)</td>
<td>16 (26.67)</td>
<td>23 (38.33)</td>
<td>21 (35.00)</td>
<td>37 (61.67)</td>
</tr>
<tr>
<td>Observation group (n=60)</td>
<td>4 (6.67)</td>
<td>29 (48.33)</td>
<td>15 (25.00)</td>
<td>12 (20.00)</td>
<td>33 (55.00)</td>
<td>48 (80.00)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.848</td>
</tr>
<tr>
<td>$p$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.028</td>
</tr>
</tbody>
</table>

### TABLE 2: COMPARISON OF ADVERSE REACTION RATES BETWEEN BOTH GROUPS (n, %)

<table>
<thead>
<tr>
<th>Group</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
<th>Thyroid dysfunction</th>
<th>Liver or kidney function damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n=60)</td>
<td>40 (66.67)</td>
<td>37 (61.67)</td>
<td>37 (61.67)</td>
<td>21 (35.00)</td>
<td>15 (25.00)</td>
</tr>
<tr>
<td>Observation group (n=60)</td>
<td>20 (33.37)</td>
<td>22 (36.67)</td>
<td>18 (30.00)</td>
<td>10 (16.67)</td>
<td>6 (10.00)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>13.333</td>
<td>7.502</td>
<td>12.117</td>
<td>5.263</td>
<td>4.675</td>
</tr>
<tr>
<td>$p$</td>
<td>0.001</td>
<td>0.006</td>
<td>0.001</td>
<td>0.022</td>
<td>0.031</td>
</tr>
</tbody>
</table>

### TABLE 3: COMPARISON OF PERIPHERAL BLOOD LYMPHOCYTE SUBSETS LEVELS BETWEEN BOTH GROUPS ($\bar{x} \pm s$)

<table>
<thead>
<tr>
<th>Group</th>
<th>CD3+ (%)</th>
<th>CD4+ (%)</th>
<th>CD8+ (%)</th>
<th>CD4+/CD8+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Control group (n=60)</td>
<td>53.47±10.23</td>
<td>59.13±8.07</td>
<td>32.86±9.33</td>
<td>38.08±8.95</td>
</tr>
<tr>
<td>Observation group (n=60)</td>
<td>52.67±10.31</td>
<td>62.27±3.16</td>
<td>32.17±9.67</td>
<td>41.10±4.87</td>
</tr>
<tr>
<td>$t$</td>
<td>0.427</td>
<td>2.896</td>
<td>0.398</td>
<td>2.296</td>
</tr>
<tr>
<td>$p$</td>
<td>0.67</td>
<td>0.005</td>
<td>0.692</td>
<td>0.023</td>
</tr>
</tbody>
</table>
NSCLC has the characteristics of high incidence, short course, poor prognosis and insidious onset, most patients often found they are in the middle and late stages, and conservative treatments such as radiotherapy, chemotherapy and immunotherapy are required to prolong their survival[7]. Currently, NSCLC treatment is mainly based on platinum drug combination therapy, with the continuous in-depth study of cancer treatment, researchers have found that some NSCLC patients can use individualized targeted therapy, but the cost is high, so the current NSCLC treatment is still dominated by cytotoxic drugs[8]. Different drug regimens have different effects and adverse reactions on patients, for improving the therapeutic effect and safety of NSCLC patients, clinical researchers have been committed to finding safe and effective treatment options.

Carboplatin is a first-line chemotherapeutic drug for cancer treatment in clinic. Its activity and anticancer spectrum are similar to those of cisplatin and it has good chemical stability, it can promote the cross-linking between Deoxyribonucleic Acid (DNA) strands and intra-strands, damage the structure of DNA molecules and then inhibit tumors growth[9]. Atezolizumab, a humanized monoclonal antibody against Programmed Cell Death 1 (PD-1), is a commonly used immunotherapeutic drug, it was launched in 2015 and has been recommended as a first-line drug for the NSCLC treatment[10]. Paclitaxel is a taxane derivative extracted from the bark of Taxus chinensis, which has a good inhibitory effect on tumor cell division and proliferation, it has an anti-tumor effect and is often used in ovarian cancer, breast cancer, NSCLC and other cancers treatment[11]. However, paclitaxel is insoluble in water, placed it in a mixed solvent of ethanol and polyoxyethyl anthracene sesame oil, since polyoxyethyl anthracene sesame oil produces histamine in the human body, there will be obvious allergic reactions to patients using this drug, pretreatment with dexamethasone, etc. is required before treatment to reduce its safety risk, increased medication may reduce patient compliance, while safety risks remain[12]. In this study, treated control group with the above three drugs, and the results indicated that the objective remission rate and disease control rate were not ideal. Albumin paclitaxel is a new type of adjuvant developed on the basis of paclitaxel and human albumin is its carrier, which can make up for the deficiencies of paclitaxel in the treatment, and has good effect and safety[13,14]. In this study, treated observation group with carboplatin, albumin paclitaxel combined with atezolizumab, the results showed that observation group possessed higher objective remission rate and disease control rate than control group (p<0.05), it shows that carboplatin, nab-paclitaxel regimen combined with atezolizumab in NSCLC treatment can improve clinical efficacy. The albumin carried by the paclitaxel molecule in the albumin paclitaxel can bind to the albumin receptor gp60 on the cell membrane, promotes the activation of caveolin on the cell membrane, paclitaxel is transferred to tumor tissue through vascular endothelial cells, reaching the interior of tumor cells and increasing its concentration, compared with paclitaxel, its anti-tumor activity is stronger and the effect is more obvious, so it can effectively control disease progression[15-18]. The albumin paclitaxel is composed of nanoparticles, which are only 1/100 of the size, and are coated by albumin, the core is a water-insoluble cytotoxic drug that does not contain cosolvents that can cause allergic reactions, so no pretreatment is required before injection, the administration time is only 30 min, which is not only convenient and simple to administer, but also increases the safety, which can reduce the adverse reactions of patients during the treatment process[19,20]. The results showed that observation group possessed lower adverse reactions than control group (p<0.05), which confirmed nab-paclitaxel is safe. Some studies have pointed out that the most important way of the body’s anti-tumor immune effect is cellular immunity,

<table>
<thead>
<tr>
<th>Group</th>
<th>CYFRA21-1 Pre-treatment</th>
<th>CYFRA21-1 Post therapy</th>
<th>SCC-Ag Pre-treatment</th>
<th>SCC-Ag Post therapy</th>
<th>CA125 Pre-treatment</th>
<th>CA125 Post therapy</th>
<th>CEA Pre-treatment</th>
<th>CEA Post therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n=60)</td>
<td>21.37±3.31</td>
<td>9.51±2.11</td>
<td>4.16±0.51</td>
<td>2.11±0.85</td>
<td>34.37±6.51</td>
<td>21.73±5.56</td>
<td>14.29±2.23</td>
<td>10.08±2.85</td>
</tr>
<tr>
<td>Observation group (n=60)</td>
<td>21.24±3.23</td>
<td>8.47±1.23</td>
<td>4.17±0.57</td>
<td>1.87±0.17</td>
<td>34.66±6.29</td>
<td>19.25±3.64</td>
<td>14.57±2.27</td>
<td>8.83±0.99</td>
</tr>
<tr>
<td>t</td>
<td>0.218</td>
<td>3.298</td>
<td>0.101</td>
<td>2.145</td>
<td>0.248</td>
<td>2.891</td>
<td>0.682</td>
<td>3.209</td>
</tr>
<tr>
<td>p</td>
<td>0.828</td>
<td>0.001</td>
<td>0.919</td>
<td>0.034</td>
<td>0.804</td>
<td>0.005</td>
<td>0.497</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**TABLE 4: COMPARISON OF SERUM TUMOR MARKER LEVELS BETWEEN BOTH GROUPS (± s, μg/l)
so lymphocyte subsets monitoring can effectively evaluate the condition of NSCLC patients\textsuperscript{[21]}. CD3\textsuperscript{+} is a unique molecular marker of T lymphocytes and exists on the surface of T lymphocytes; CD4\textsuperscript{+} is an important cell that regulates the immune response and plays an auxiliary/inducing role in the process of anti-tumor immunity. Its secretion can effectively enhance the immune function of cells, make B cells proliferate and promote antibody production; CD8\textsuperscript{+} is a cytotoxic T cell whose co-receptor is mainly expressed on the surface, which can inhibit humoral and cellular immunity, and its increased secretion provides the basic conditions for the metastasis and proliferation of tumor cells\textsuperscript{[22,23]}. When CD4\textsuperscript{+}/CD8\textsuperscript{+} are in balance, it means that the immune response of the body is normal. If the ratio decreases, it means that the immune function of the body is also reduced. In this study, observation group possessed higher CD3\textsuperscript{+}, CD4\textsuperscript{+} and CD4\textsuperscript{+}/CD8\textsuperscript{+} values than control group, but it possessed lower CD8\textsuperscript{+} values than control group (p<0.05), it shows that carboplatin, nab-paclitaxel regimen combined with atezolizumab in NSCLC treatment can improve the immune function of the body. Because albumin paclitaxel can stimulate macrophages to polarize them to M1, prevent them from polarizing to M2, improve the immunosuppressive state of NSCLC patients and improve the immune function of the body\textsuperscript{[24]}. Moreover, CYFRA21-1, SCC-Ag, CA125 and CEA are important tumor markers, which are highly expressed in many cancer diagnoses. Therefore, the above indicators can be used for evaluating the condition of NSCLC patients. In this study, observation group possessed lower various tumor markers levels than control group after treatment (p<0.05), it indicates that carboplatin; nab-paclitaxel regimen combined with atezolizumab in NSCLC treatment can promote tumor cell apoptosis. Because albumin paclitaxel encapsulates paclitaxel to increase its affinity for tumors, after albumin binds to the vascular endothelial cell membrane, paclitaxel enters cells through phagocytosis, the increased uptake of paclitaxel by tumor cells can inhibit tumor cells mitosis and prevent spindles formation, strengthening the killing effect on tumor cells can reduce tumor markers levels\textsuperscript{[25]}. In summary, the carboplatin, nab-paclitaxel regimen combined with atezolizumab has a good curative effect in NSCLC treatment, can improve the body’s immune function, promote the improvement of the treatment effect and also reduce adverse reactions, with good safety.

Authors’ contributions:
Li Li and Zhensheng Xu have contributed same to this work.

Conflict of interests:
The authors declared no conflict of interests.

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