Effect of paclitaxel liposome combined with nedaplatin on serum HE4, CA125, CA19–9, AFP, CEA and T lymphocyte subsets in patients with advanced ovarian cancer

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Objective: To study the effect of paclitaxel liposome combined with nedaplatin on serum HE4, CA125, CA19-9, AFP, CEA and T lymphocyte subsets in patients with advanced ovarian cancer. Methods: A total of 80 patients with advanced ovarian cancer in our hospital from December 2012 to December 2015 were enrolled in this study. The subjects were divided into control group (n=40) and experiment group (n=40) randomly. The control group were treated with paclitaxel and cisplatin, the experiment group were treated with paclitaxel liposome combined with nedaplatin. 21 days for a period of treatment and the two groups were treated for 3 periods. The serum HE4, CA125, CA19-9, AFP, CEA levels and peripheral blood CD3+ CD4+, CD8+ and NK cells of the two groups before and after treatment were compared. Results: There were no significantly differences of the serum HE4, CA125, CA19-9, AFP, CEA level and peripheral blood CD3+, CD4+, CD8+ and NK cells of the two groups before treatment (P>0.05). The serum HE4, CA125, CA19-9, AFP and CEA level of the two groups after treatment were significantly lower than before treatment (P<0.05), and that of experiment were significantly lower than control group (P<0.05). The peripheral blood CD3+, CD4+, CD8+ and NK cells of the two groups after treatment were significantly lower than before treatment (P<0.05), and that of experiment were significantly higher than control group (P<0.05). Conclusions: Paclitaxel liposome combined with nedaplatin can significantly reduce the serum HE4, CA125, CA19-9, AFP and CEA levels, improve peripheral blood CD3+, CD4+, CD8+ and NK levels of patients with advanced ovarian cancer, and it was worthy clinical application.

1. Introduction

Ovarian cancer is a common malignant tumor with high mortality in the female reproductive system, and is a serious threat to women's life and health[1]. With the increasing pressure of living and diet structure, the incidence of ovarian cancer increased year by year, reaching more than 5%, and the 5 year survival rate of Ovarian cancer patients is only about 30%[2,3]. Because there is no significant clinical symptoms in the early stage of ovarian cancer, the patient often has a late stage of ovarian cancer in clinical diagnosis, and the disease progression is rapid, malignant tumor cells often have spread to the uterus, the greater part of the retina, attachment, so the treatment is difficult and the prognosis is poor[4,5]. At present, the clinical treatment of patients with advanced ovarian cancer often use chemotherapy, and paclitaxel combined with cisplatin chemotherapy is the first-line treatment of advanced ovarian cancer, but it has a strong gastrointestinal toxicity, thus limiting its clinical application[6]. Lipusu is the liposome of paclitaxel, it-overcomes the characteristics of paclitaxel, which is difficult to dissolve in water, and has a lower adverse reaction[7]. Nedaplatin is a second generation platinum drug with lower gastrointestinal toxicity and neurotoxicity[8]. This study aims to examine the effect of paclitaxel liposome combined with nedaplatin on serum HE4, CA125, CA19-9, AFP, CEA and T lymphocyte subsets in patients with advanced ovarian cancer. The results are as follows.
2. Materials and methods

2.1. General information

A total of 80 patients with advanced ovarian cancer in our hospital from December 2012 to December 2015 were selected as study subjects. Case inclusion criteria: (1) Age greater than or equal to 18 years; (2) The pathology and cytology for patients with advanced ovarian cancer; (3) Never received any chemotherapy treatment before. Case exclusion criteria: (1) Patients with other malignant tumors; (2) Person whose heart, lung, liver, kidney can't functions very well; (3) Patients with chemotherapy contraindication; (4) Women in pregnancy or lactation; (5) Patients who do not cooperate with the treatment.

All patients were randomly divided into experimental group and control group, each of 40 cases. The control group were aged from 36 to 62 years old, mean age (51.32±9.75) years old; Weight 45-72 kg, mean weight (54.38±14.61) kg; Tumor types: 12 cases of mucinous cystadenocarcinoma, 8 cases of endometrioid carcinoma, 18 cases of Serous cystadenocarcinoma, 2 cases of transitional-cell carcinoma; Pathological stage: 29 cases of stage III, 11 cases of stage IV. The experience group were aged from 37 to 61 years old, mean age (50.41±10.37) years old; Weight 45-71 kg, mean weight (53.92±15.14) kg; Tumor types: 11 cases of mucinous cystadenocarcinoma, 7 cases of endometrioid carcinoma, 20 cases of Serous cystadenocarcinoma, 2 cases of transitional-cell carcinoma; Pathological stage: 31 cases of stage III, 9 cases of stage IV. There were no significant differences in age, weight, tumor type and pathological stage between the two groups (P>0.05). All patients were informed consent and voluntarily joined in this study, and were approved by the hospital ethics committee.

2.2. Experimental methods

Patients in the control group were given TC chemotherapy, specifically for: Paclitaxel (Purchased from Haikou Pharmaceutical Factory, Specification 60 mg/film, Chinese medicine standard word H20083850), Intravenous infusion, 70 mg/m², d1, and hydrated with normal saline 2 000 mL, 21 d for 1 courses. Two groups of patients were collected before and after the treatment with fasting venous blood 5 mL, serum separation, the levels of human epididymal protein 4 (HE4), cancer antigen 125 (CA125), cancer antigen 19-9 (CA19-9), α-fetoprotein (AFP), carcinoembryonic antigen (CEA), CD3⁺, CD4⁺, CD8⁺ and the ratio of natural killer (NK) cells were detected and compared between the two groups before and after treatment.

Detection of HE4 levels was used a double sandwich enzyme-linked immunosorbent assay (ELISA) kit, and the instrument is fully automated immunoassay analyzer Abbott, all operations are carried out in strict accordance with the kit instructions; The levels of CA125, CA19-9, AFP and CEA were detected by chemiluminescence immunoassay, and the instrument used was Beckman Coulter Unicel Dxl 800 immunoassay analyzer; Peripheral blood CD3⁺, CD4⁺, CD8⁺ and NK cells were detected by FACSCalibur BD automatic multi color analysis flow cytometry. Tumor markers HE4, CA125, CA19-9, AFP and CEA positive criteria were: HE4>150 pmol/L, CA125>35 U/mL, CA19-9>37 U/mL, AFP>10 μg/L and CEA>6 μg/L[9,10].

2.4. Statistical method

By using SPSS19.0 software package, measurement data were expressed as mean ± standard deviation, t test was used to compare between groups of measurement data and count data, with P<0.05 as statistically significant difference.

3. Results

3.1. Comparison of serum HE4, CA125 and CA19-9 levels

Table 1
Comparison of serum HE4, CA125 and CA19-9 levels before and after treatment in two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>40</td>
<td>279.36±24.38</td>
<td>216.51±43.17</td>
</tr>
<tr>
<td>Experimented group</td>
<td>40</td>
<td>72.37±16.57</td>
<td>34.43±20.35</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, *P<0.05; compared with the control group, +P<0.05.
**before and after treatment between the two groups**

Before treatment, there was no significant difference in serum HE4, CA125 and CA19-9 levels between the two groups \( (P>0.05) \); After treatment, the level of serum HE4, CA125 and CA19-9 of the two groups were significantly lower than those before treatment, at the same time, the experimental group patients were significantly lower than the control group \( (P<0.05) \) (Table 1).

**3.2. Comparison of serum levels of AFP and CEA before and after treatment in two groups**

Before treatment, there was no significant difference in the serum levels of AFP and CEA between the two groups \( (P>0.05) \); After treatment, for both experimental group and control group, the level of AFP and CEA were significantly lower than those of before treatment. At the same time, those indexes of the experimental group were significantly lower than those of the control group \( (P<0.05) \) (Table 2).

**Table 2**

Comparison of serum levels of AFP and CEA before and after treatment in two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>40</td>
<td>86.42±7.41</td>
<td>9.34±2.31 ²</td>
</tr>
<tr>
<td>Experimental</td>
<td>40</td>
<td>85.93±8.34</td>
<td>3.31±1.04 ²</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, \( P<0.05 \); compared with the control group, \( P<0.05 \).

**3.3. Comparison of peripheral blood T lymphocyte subsets and NK cell level before and after treatment in two groups**

Before treatment, there was no significant difference in the ratio of peripheral blood CD3⁺, CD4⁺, CD8⁺ and NK cells in the two groups \( (P>0.05) \); After treatment, the ratio of CD3⁺, CD4⁺, CD8⁺ and NK cells in peripheral blood of the two groups was significantly lower than that before treatment. At the same time, the immune function of patients in experimental group were significantly higher than the control group \( (P<0.05) \) (Table 3).

**4. Discussion**

Ovarian cancer is a kind of chemotherapy sensitive tumor, so the clinical treatment of patients with advanced ovarian cancer is mainly chemotherapy\[11\]. Paclitaxel combined with cisplatin TC chemotherapy regimen is a first-line treatment for advanced ovarian cancer, but the water solubility of paclitaxel is poor, which often causes adverse reactions. Cisplatin is the first generation of platinum anticancer drugs, which has strong Gastrointestinal toxicity and neurotoxicity\[12\]. Lipusu is one paclitaxel liposome, it overcomes the shortcomings of the poor water solubility of paclitaxel, which has a low adverse reaction, and has a relatively long half-life. Nedaplatin is a new type of platinum drugs, which has a mechanism of action similar to that of cisplatin, and it has high cytotoxicity to ovarian cancer cells, but the digestive tract toxicity and renal toxicity is small\[13\]. HE4, CA125, CA19-9, AFP and CEA are clinically recognized as the serum tumor markers of ovarian cancer, they are commonly used in early diagnosis, the judgment for therapeutic efficacy and prognosis of ovarian cancer. HE4 is a secreted protein of Whey acidic protein family, it has a high degree of sensitivity and specificity for ovarian epithelial cells, and is highly expressed in epithelial ovarian cancer cells\[14\]. CA125 is highly expressed in serous ovarian cancer, and shows an increasing trend with the development of ovarian cancer\[15\]. CA19-9 is a kind of lipid which exists in the cell membrane in the form of mucin, and with the development of ovarian cancer, the level of serum is gradually increased\[16\]. AFP is a globular protein expressed in the yolk sac of the embryo, which is a specific marker of liver cancer, and the expression level of AFP in ovarian cancer was also increased with the progression of the disease\[17\]. CEA is a broad spectrum non-specific tumor marker, and it also has a small amount of expression in ovarian cancer tissues\[18\]. This study examines the effect of paclitaxel liposome combined with nedaplatin on serum HE4, CA125, CA19-9, AFP, CEA and T lymphocyte subsets in patients with advanced ovarian cancer, so that we can provide a clinical basis for the clinical application in patients with Lipusu combined with nedaplatin in the treatment of advanced ovarian cancer.

This study shows that before treatment, there was no significant difference in the level of serum HE4, CA125, CA19-9, AFP and CEA between the two groups \( (P>0.05) \), but after treatment, the level of serum HE4, CA125, CA19-9, AFP and CEA between the two groups were significantly lower than those before treatment, at the same time, the tumor markers of the experimental group was significantly lower than that of the control group \( (P<0.05) \). It suggests that the treatment using Lipusu combined with nedaplatin can significantly lower the serum of patients with ovarian cancer HE4, CA125, CA19-9, AFP and CEA. Lipusu is paclitaxel liposome, it can lead to the formation of microtubule polymerization in tumor cells, hinder the normal mitosis of tumor cells, cause cancer cells

**Table 3**

Comparison of peripheral blood T lymphocyte subsets and NK cell level before and after treatment in two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>40</td>
<td>71.36±8.45</td>
<td>35.31±4.21 ²</td>
</tr>
<tr>
<td>Experimental</td>
<td>40</td>
<td>70.14±9.33</td>
<td>53.17±5.20 ²</td>
</tr>
</tbody>
</table>

Note: compared with before treatment, \( P<0.05 \); compared with the control group, \( P<0.05 \).
to die, so as to play the role of anti-tumor[19]. Nedaplatin is a new type of platinum anticancer drugs, it can generate a variety of ionic substances to the combination of tumor cells DNA, which inhibits DNA replication process, thus playing an anti tumor effect[20]. The combination of Lipusu with nedaplatin can play a synergistic anti-tumor effect, and has a strong killing effect on ovarian cancer cells, reflecting that the levels of serum tumor markers HE4, CA125, CA19-9, AFP and CEA were significantly decreased. This study also shows that before treatment, there was no significant difference in the ratio of peripheral blood CD3\(^+\), CD4\(^+\), CD8\(^-\) and NK cells in the two groups (P<0.05); After treatment, the ratio of CD3\(^+\), CD4\(^+\), CD8\(^-\) and NK cells in peripheral blood of the two groups was significantly lower than that before treatment. At the same time, the immune function of patients in experimental group were significantly higher than the control group (P<0.05). It suggests that the treatment using Lipusu combined with nedaplatin can improve the immune function of patients with advanced ovarian cancer. This may be because that Lipusu activate the immune system in vivo from patients with ovarian cancer of monocyte macrophages after phagocytosis of endothelial system, in the end the immune function of patients can be improved to a certain extent[21].

In summary, the treatment using Lipusu combined with nedaplatin can significantly reduce the levels of serum HE4, CA125, CA19-9, AFP and CEA in patients with advanced ovarian cancer, improve the level of T lymphocyte subsets, improve the immune function of patients, and It is worth popularizing in clinic.

References