Effect of Herceptin combined with paclitaxel neoadjuvant chemotherapy on the proliferation viability of HER-2 positive breast cancer cell

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ARTICLE INFO

Objective: To study the effect of Herceptin combined with paclitaxel neoadjuvant chemotherapy on the proliferation viability of HER-2 positive breast cancer cell. Methods: The patients who were diagnosed with breast cancer and received neoadjuvant chemotherapy in Ziyang First People’s Hospital between February 2015 and October 2017 were selected and randomly divided into the experimental group who received Herceptin combined with docetaxel chemotherapy and the control group who received epirubicin combined with docetaxel chemotherapy. After chemotherapy ended, serum levels of tumor markers were measured; after surgical resection, the breast cancer lesions were collected to measure the mRNA expression of proliferation genes and tumor suppressor genes. Results: The differences in tumor marker levels as well as proliferation gene and tumor suppressor gene expression were statistically significant between the two groups; CA15-3, IGF-1, TSGF and TPS levels in serum as well as CyclinD1, PCNA, Bcl-2, Survivin and VEGF mRNA expression in breast cancer lesions of experimental group were lower than those of control group whereas PTEN, Bax, ARID1A, FasL, and Caspase-3 mRNA expression in breast cancer lesions were higher than those of control group. Conclusion: Herceptin combined with paclitaxel neoadjuvant chemotherapy can more effectively inhibit the proliferation activity of HER-2 positive breast cancer cells than epirubicin combined with paclitaxel chemotherapy.

I. Introduction

Brgical resection can help reduce tumor volume and depth of infiltration, which is conducive to radical resection of the lesion by surgery[1]. Epirubicin and docetaxel are common drugs for breast cancer chemotherapy. The former has the effect of interfering with cell cycle, the latter has the effect of destroying the microtubule system, and their combination can inhibit the growth of breast cancer cells through different mechanisms[2]. Human epidermal growth factor receptor-2 (HER-2) is a molecule that plays an important role in the pathological process of breast cancer. Approximately 1/5-1/4 of breast cancer patients have positive HER-2 in their lesions, and the efficacy of epirubicin and docetaxel chemotherapy is not ideal for patients with HER-2-positive breast cancer[3]. Herceptin is a recombinant humanized monoclonal antibody that can specifically recognize and bind HER-2 to inhibit HER-2-mediated tumor growth effect and inhibit tumor cell growth[4]. In the following studies, we specifically analyzed the effect of herceptin combined with paclitaxel neoadjuvant chemotherapy on the proliferation activity of HER-2-positive breast cancer cells.

2. Case information and research methods

2.1 General case information

The patients who were newly diagnosed with breast cancer in Ziyang First People’s Hospital between February 2015 and October 2017 were selected as the research subjects, they were diagnosed with HER-2-positive breast cancer by pathology biopsy and conformed to the indications of surgical resection and neoadjuvant chemotherapy, and the patients with surgery or chemotherapy contraindications and those who had underwent anti-tumor treatment before inclusion were ruled out. A total of 124 patients were enrolled and divided into the experimental group and the
control group by the random number table method, with 62 patients in each group. In the experimental group, there were 38 male patients and 24 female patients with the age range of 37-64 years and an average age of (50±8) years; in the control group: there were 36 male patients and 26 female patients with the age range of 36-65 years and an average age of (49±7) years. There was no significant difference in the general data between the two groups (P>0.05).

2.2 Chemotherapy methods

The two groups were given oral administration of 9.0 mg of dexamethasone at 12 h and 6 h before chemotherapy, and intramuscular injection of 20 mg of diphenhydramine and 10 mg of dexamethasone injection at 0.5 h before chemotherapy. The chemotherapy regimens of the experimental group were as follows: 75 mg/m² docetaxel, intravenous drip, on day 1, trastuzumab 8 mg/kg (cycle 1) or 6 mg/kg (cycle 2-4), intravenous drip, on day 2, for four consecutive cycles of chemotherapy. The chemotherapy regimens of the control group were as follows: epirubicin 80 mg/m², intravenous drip, on day 1, docetaxel 75 mg/m², intravenous drip, on day 1, for 4 consecutive cycles of chemotherapy.

2.3 Serum tumor marker detection

After the end of chemotherapy, 3-5 mL of venous blood was collected in the morning on an empty stomach to separate serum, and the instructions of the enzyme-linked immunosorbent kit were referred to determine the levels of CA15-3, IGF-1, TSGF and TPS.

2.4 Gene mRNA expression detection

Surgically removed breast cancer lesions were collected, kits were used to extract the RNA from the lesions and reversely transcribe it into cDNA; then fluorescent quantitative PCR kit was used to amplify cDNA, the adopted primers were the specific primers of CyclinD1, PCNA, Bcl-2, Survivin, VEGF, PTEN, Bax, ARID1A, FasL and Caspase-3; the mRNA expression levels of the above genes were calculated according to the PCR curves.

2.5 Statistical methods

SPSS 20.0 software was used to input data and conduct normality analysis, the measurement data conforming to normal distribution were analyzed by t test, and the difference in analysis results was statistically significant if P<0.05.

3. Results

3.1 Serum tumor markers CA15–3, IGF–1, TSGF and TPS levels

Analysis of serum tumor markers CA15-3, IGF-1, TSGF and TPS levels between experimental group and control group was as follows: the difference in tumor marker levels was statistically significant between the two groups (P<0.05), and CA15-3, IGF-1, TSGF and TPS levels in serum of experimental group were lower than those of control group.

3.2 Proliferation gene expression in breast cancer lesions

Analysis of proliferation genes CyclinD1, PCNA, Bcl-2, Survivin and VEGF expression in breast cancer lesions between experimental group and control group was as follows: the difference in proliferation gene mRNA expression was statistically significant between the two groups (P<0.05), and CyclinD1, PCNA, Bcl-2, Survivin and VEGF mRNA expression in breast cancer lesions of experimental group were lower than those of control group.

3.3 Tumor suppressor gene expression in breast cancer lesions

Analysis of tumor suppressor genes PTEN, Bax, ARID1A, FasL and Caspase-3 expression in breast cancer lesions between experimental group and control group was as follows: the difference in tumor suppressor gene mRNA expression was statistically significant between the two groups (P<0.05), and PTEN, Bax, ARID1A, FasL and Caspase-3 mRNA expression in breast cancer lesions of experimental group were higher than those of control group.

4. Discussion

HER-2 is a receptor that plays an important role in the pathological process of breast cancer, and it can promote the growth of breast cancer cells through the transduction of downstream signaling pathways. Positive expression of HER-2 in breast cancer lesions can shorten the patients’ survival and increase recurrence and metastasis rates[5,6]. Epirubicin and docetaxel are the common neoadjuvant chemotherapy drugs for breast cancer patients, but their efficacy

Table 1. Comparison of serum tumor markers between the two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>CA15-3 (U/mL)</th>
<th>IGF-1 (ng/mL)</th>
<th>TSGF (U/L)</th>
<th>TPS (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group</td>
<td>12.36±1.85</td>
<td>47.62±6.71</td>
<td>39.56±5.57</td>
<td>57.52±6.78</td>
</tr>
<tr>
<td>Control group</td>
<td>17.62±2.34</td>
<td>58.69±7.74</td>
<td>55.32±7.04</td>
<td>69.24±7.93</td>
</tr>
<tr>
<td>t</td>
<td>13.885</td>
<td>8.509</td>
<td>13.823</td>
<td>8.845</td>
</tr>
<tr>
<td>P</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
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</tbody>
</table>
in killing cancer cells is limited for HER-2-positive breast cancer. Herceptin is a humanized monoclonal antibody against HER-2, which can selectively act on the extracellular part of HER-2, block the activation of the downstream signal pathway of the receptor and inhibit the biological effect mediated by the receptor to inhibit tumor growth[7,8]. In the growth process of malignant tumor lesions, the tumor itself can synthesize and secrete multiple molecules into the blood circulation, which is a marker of tumor growth. CA15-3, IGF-1, TSGF and TPS are the tumor markers closely related to breast cancer at present[9,10]. In the study, in order to define the killing effect of herceptin combined with paclitaxel neoadjuvant chemotherapy on HER-2-positive breast cancer cells, we first analyzed the changes of tumor markers after chemotherapy, and the results showed that compared with those of control group, serum CA15-3, IGF-1, TSGF and TPS levels of experimental group were significantly lower after chemotherapy. This suggests that herceptin combined with paclitaxel neoadjuvant chemotherapy is more effective than epirubicin combined with paclitaxel chemotherapy in inhibiting the expression of proliferation genes in HER-2-positive breast cancer cells and thereby hindering the proliferation of tumor cells.

The abnormal proliferation of breast cancer cells is also related to the expression reduction or deletion of various tumor suppressor genes. The loss of tumor suppressor genes’ function will hinder cell apoptosis and enhance its proliferation activity. PTEN is a molecule with dephosphorylation activity, which inactivates the signal molecules in the PI3K/AKT pathway by dephosphorylation, thereby weakening the proliferation effect mediated by this pathway[16]; Bax is a pro-apoptotic molecule in the bcl-2 family, which can form dimers with the proliferation molecule Bcl-2 in the family and hinder its pro-proliferation effect to inhibit cell proliferation and promote cell apoptosis[17,18]; ARID1A is an upstream regulatory signal molecule of the death receptor pathway, which can promote the generation of Fas and initiate the apoptotic pathway by binding with FasL[19]; Caspase-3 is a common downstream effector molecule in cells with different apoptosis mechanisms, which can directly act on the nucleus, promote apoptosis and hinder cell proliferation[20].

Our analysis of the above tumor suppressor gene expression in breast cancer lesions confirmed that compared with the tumor suppressor gene expression in breast cancer lesions of control group, the mRNA expression levels of CyclinD1, PCNA, Bcl-2, Survivin and VEGF of experimental group were significantly lower. This suggests that herceptin combined with paclitaxel neoadjuvant chemotherapy is more effective than epirubicin combined with paclitaxel chemotherapy in inhibiting the expression of proliferation genes in HER-2-positive breast cancer cells and thereby hindering the proliferation of tumor cells.

Table 2.
Comparison of proliferation genes in breast cancer lesions between the two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>CyclinD1</th>
<th>PCNA</th>
<th>Bcl-2</th>
<th>Survivin</th>
<th>VEGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group</td>
<td>0.68±0.09</td>
<td>0.58±0.07</td>
<td>0.71±0.08</td>
<td>0.62±0.06</td>
<td>0.54±0.09</td>
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<tr>
<td>Control group</td>
<td>1.00±0.17</td>
<td>1.00±0.13</td>
<td>1.00±0.19</td>
<td>1.00±0.22</td>
<td>1.00±0.15</td>
</tr>
<tr>
<td>t</td>
<td>12.690</td>
<td>22.398</td>
<td>11.076</td>
<td>13.121</td>
<td>20.706</td>
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<tr>
<td>P</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 3.
Comparison of tumor suppressor genes in breast cancer lesions between the two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>PTEN</th>
<th>Bax</th>
<th>ARID1A</th>
<th>FasL</th>
<th>Caspase-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group</td>
<td>1.77±0.25</td>
<td>1.59±0.22</td>
<td>1.46±0.19</td>
<td>1.93±0.26</td>
<td>1.83±0.29</td>
</tr>
<tr>
<td>Control group</td>
<td>1.00±0.14</td>
<td>1.00±0.09</td>
<td>1.00±0.18</td>
<td>1.00±0.20</td>
<td>1.00±0.16</td>
</tr>
<tr>
<td>P</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>
chemotherapy in increasing the expression of tumor suppressor genes in HER-2-positive breast cancer cells and thus inducing the apoptosis of tumor cells.

Based on the above analysis of tumor marker levels and gene expression, preliminary conclusion can be drawn: herceptin combined with paclitaxel neoadjuvant chemotherapy for HER-2-positive breast cancer can more effectively inhibit the proliferation activity of breast cancer cells in the lesions than epirubicin combined with paclitaxel chemotherapy.

References


