Effect of cisplatin-based concurrent radiochemotherapy on malignant degree of advanced cervical cancer and expression of proto-oncogene and tumor suppressor genes

Rui-Juan Jia¹, Yang Zhang², Ju-Lang Dong¹, Jun Wei³

¹ Department of Obstetrics and Gynecology, the Second People’s Hospital of Foshan, Foshan 528000, China
² Radiotherapy Department No. 1 of Cancer Center, the First People’s Hospital of Foshan, Foshan 528000, China
³ Department of Gastrointestinal Surgery, the Second People’s Hospital of Foshan, Foshan 528000, China

Objective: To study the effect of cisplatin-based concurrent radiochemotherapy on the malignant degree of advanced cervical cancer and the expression of proto-oncogene and tumor suppressor genes. Methods: A total of 82 patients with advanced cervical cancer who were treated in our hospital between July 2013 and December 2016 were collected and divided into control group and observation group according to random number table, with 41 cases in each group. The control group of patients received radiotherapy alone, while the observation group of patients received cisplatin-based concurrent radiochemotherapy. Tumor marker levels in serum as well as proto-oncogene and tumor suppressor gene expression in tumor tissue were compared between two groups of patients before and after treatment. Results: Before treatment, differences in tumor marker levels in serum as well as proto-oncogene and tumor suppressor gene expression in tumor tissue were not statistically significant between two groups of patients. After treatment, serum tumor markers SCC, CA50, CA724 and CEA levels of observation group were significantly lower than those of control group; proto-oncogene DEK, c-myc and PIK3CA mRNA expression in tumor tissue were significantly lower than those of control group; tumor suppressor genes p53, SOCS-1, FHit and PTEN mRNA expression in tumor tissue were significantly higher than those of control group. Conclusions: Cisplatin-based concurrent radiochemotherapy can effectively reduce the tumor malignancy and balance the proto-oncogene / tumor suppressor gene expression in patients with advanced cervical cancer.

1. Introduction

Cervical cancer is the most common malignant tumor disease in women, its early clinical manifestations are not obvious, and it has reached middle-advanced stage when there is obvious vaginal irregular bleeding[1,2]. How to improve the treatment effect of advanced cervical cancer patients and prolong their quality of life has been the focus of obstetric and gynecological research. Radiation therapy is the most common therapy for advanced cervical cancer, and the total pelvic anterior posterior-field vertical radiotherapy can effectively kill the metastatic lesions. However, some studies have also pointed out that radiotherapy alone has limitations in inhibiting the growth of tumor, and tumor cell sensitivity to chemotherapy declines with the extension of cycle. Cisplatin is the most common chemotherapy drug in clinical practice, and the studies in recent years have found that its application can increase the local tumor tissue sensitivity to radiotherapy, so many scholars recommend cisplatin-based concurrent radiochemotherapy as the preferred therapy for patients with advanced cervical cancer[3,4]. In this study, the effects of radiotherapy alone and concurrent chemoradiotherapy on the malignancy of advanced cervical cancer were compared in order to lay a practical foundation for the selection of therapy for future similar diseases, hereby reported as follows.
2. Materials and methods

2.1. Case information

A total of 82 patients with advanced cervical cancer who were treated in our hospital between July 2013 and December 2016 were selected as the research subjects, and the patients themselves or the family members signed informed consent form. According to random number table, the enrolled patients were divided into control group and observation group, with 41 cases in each group. Control group were 48-76 years old, and the body weight was 49.70 kg and (59.82±9.71) kg on average; observation group were 46-78 years old, and the body weight was 47-71 kg and (59.53±9.69) kg on average. The differences in age and weight distribution of the two groups were not statistically significant (P>0.05), and the hospital ethics committee approved the study.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with primary cervical cancer by pathological biopsy, and with advanced tumor stage; (2) diagnosed for the first time, and receiving no systematic treatment before; (3) with complete clinical data. Exclusion criteria: (1) associated with primary malignant tumors of other tissue organs; (2) combined with systemic infectious diseases; (3) combined with serious autoimmune disease.

2.3. Therapy

Control group of patients received conventional radiotherapy, including the total pelvic anterior posterior-field vertical radiotherapy, 2 G yarn/time, 5 times/week, and total dose 45-50 Gy. Observation group of patients, based on conventional radiotherapy, received the cisplatin-based chemotherapy, specifically as follows: Observation group of patients were given 40 mg of cisplatin (produced by Guizhou Hanfang Pharmaceutical Co., Ltd., Approval No. H20020273) by intravenous drip one time every week with a total of 5-6 times.

2.4 Tumor markers

Before and after treatment, 2.0 mL of fasting cubital venous blood was extracted from two groups of patients. After anticoagulation treatment the fasting cubital venous blood was let stand at room temperature for stratification and centrifuged at 2 500 r/min for 10-15 min to take the upper serum, and enzyme-linked immunosorbent assay was used to determine serum levels of tumor markers squamous cell carcinoma antigen (SCC), carbohydrate antigen 50 (CA50), carbohydrate antigen 724 (CA724) and carcinoembryonic antigen (CEA).

2.5 Proto-oncogene and tumor suppressor gene expression

Before and after treatment, cervical cancer tissue samples were collected respectively, added in Trizol reagent (produced by Shenzhen Abio Technology Development Co., Ltd., type a-162) to split the cells, joined by chloroform (produced by Nanjing Saihongrui Biotechnology Co., Ltd., the article number a-shr-2054) and then centrifuged at high speed to take the upper clear water phase. The same volume of isopropanol was used to precipitate the total RNA in it and 75% ethanol (produced by Shanghai Huzhen Industrial Co., Ltd., article number XW-RS-028) was used clean and then dry the precipitation. Reverse transcription kit (produced by Shanghai Shanran Biotechnology Co., Ltd., the article number of TQ2601-01) instructions were followed to synthesize cDNA samples, and the fluorescence quantitative PCR kit (produced by Chengdu Foregene Biotechnology Co., Ltd., model QP-0201T) instructions were followed for mRNA amplification of proto-oncogenes DEK, c-myc and PIK3CA as well as tumor suppressor genes p53, SOCS-1, FHIT and PTEN. The corresponding PCR amplification curve was obtained in computer software and the mRNA expression of the target genes were calculated.

2.6 Statistical processing

The data in the study were processed by software SPSS 20.0. Tumor markers, proto-oncogene mRNA expression and tumor suppressor gene mRNA expression belonged to measurement data and were in terms of mean ± standard deviation, and the comparison was performed by t test. Statistical value P<0.05 was the standard of statistical significance in differences.

3. Results

3.1 Serum tumor markers before and after treatment

Before and after treatment, comparison of serum tumor markers SCC (ng/mL), CA50 (U/mL), CA724 (U/mL) and CEA (μg/L) levels between two groups of patients was as follows: serum SCC, CA50, CA724 and CEA levels were not significantly different between two groups of patients before treatment (P>0.05); compared with those before treatment, serum SCC, CA50, CA724 and CEA levels of both groups were decreased significantly after treatment (P<0.05); compared with those of control group, serum SCC, CA50, CA724 and CEA levels of observation group were decreased significantly after treatment (P<0.05), shown in Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>SCC</th>
<th>CA50</th>
<th>CA724</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>41</td>
<td>Before treatment</td>
<td>6.72±0.75</td>
<td>49.83±6.27</td>
<td>29.85±3.74</td>
<td>9.12±0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>3.18±0.43</td>
<td>34.76±4.46</td>
<td>21.63±2.88</td>
<td>6.07±0.78</td>
</tr>
<tr>
<td>Observation group</td>
<td>41</td>
<td>Before treatment</td>
<td>6.69±0.72</td>
<td>49.76±6.42</td>
<td>29.79±3.61</td>
<td>9.07±0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>1.76±0.21*</td>
<td>20.53±2.79*</td>
<td>12.07±1.86*</td>
<td>2.58±0.34*</td>
</tr>
</tbody>
</table>

Note: compared with the same group before treatment, *P<0.05; compared with control group after treatment, †P<0.05.

Table 1. Comparison of serum SCC, CA50, CA724 and CEA levels before and after treatment.
3.2. Proto-oncogene mRNA expression

Before and after treatment, comparison of proto-oncogene DEK, c-myc and PIK3CA mRNA expression in tumor tissue between two groups of patients was as follows: DEK, c-myc and PIK3CA mRNA expression in tumor tissue were not significantly different between two groups of patients before treatment (P>0.05); compared with those before treatment, DEK, c-myc and PIK3CA mRNA expression in tumor tissue of both groups were decreased significantly after treatment (P<0.05); compared with those of control group, DEK, c-myc and PIK3CA mRNA expression in tumor tissue of observation group were decreased significantly after treatment (P<0.05), shown in Table 2.

3.3 Tumor suppressor gene mRNA expression

Before and after treatment, comparison of tumor suppressor genes p53, SOCS-1, FHIT and PTEN mRNA expression in tumor tissue between two groups of patients was as follows: p53, SOCS-1, FHIT and PTEN mRNA expression in tumor tissue were not significantly different between two groups of patients before treatment (P>0.05); compared with those before treatment, p53, SOCS-1, FHIT and PTEN mRNA expression in tumor tissue of both groups were increased significantly after treatment (P<0.05); compared with those of control group, p53, SOCS-1, FHIT and PTEN mRNA expression in tumor tissue of observation group were increased significantly after treatment (P<0.05), shown in Table 3.

4. Discussion

Radiotherapy is the main therapy for the advanced cervical cancer at present, and for the patients with abdominal metastasis, pelvic expanded radiotherapy can be used to kill metastatic lesions and reduce tumor malignancy[5,6]. With radiation application popularization, many cases have shown that radiation time is negatively correlated with the sensitivity of tumor cells, and how to maintain radiation effect and further curb tumor growth is the focus of current clinical research. Cisplatin is the most common platinum drug in the clinical practice, which is combined with intracellular nucleophilic genes to interfere with the normal replication of the DNA, and thereby inhibit the proliferation of tumor cells. Studies have also shown that cisplatin can increase the radiation sensitivity, and help to consolidate and enhance the therapeutic effect of radiotherapy for advanced cervical cancer, and therefore, cisplatin-based concurrent radiochemotherapy has attracted extensive attention[7,8]. In order to define the different clinical effects of radiotherapy alone and concurrent radiochemotherapy, tumor marker levels in serum as well as proto-oncogene and tumor suppressor gene expression in tumor tissue were compared between two groups of patients before and after treatment in the study, and the specific results remain to be specifically analyzed in the study below.

Tumor markers are the most common indicators that help to diagnose malignant tumor and judge the severity, and there is the abnormal expression of a variety of specific and broad-spectrum tumor markers in circulating blood of patients with cervical cancer, thus detection of their levels can objectively reflect the macro effect of different treatments[9,10]. SCC has a higher specificity for the diagnosis of cervical cancer, mostly expressed in squamous cell epithelium, and its content is highly consistent with the malignant degree of cervical cancer[11]. CA50, CA724 and CEA are all broad-spectrum tumor markers, and their expression increases in gastric cancer, liver cancer, colorectal cancer, and other malignancies[12]. In the study, serum levels of above tumor markers were compared between the two groups of patients before and after treatment, and it was found that compared with those before treatment, serum SCC, CA50, CA724 and CEA levels of both groups were lower after treatment, showing that both kinds of treatments can macroscopically reduce tumor malignancy. Further compared with the control group, observation group were with lower serum levels of SCC, CA50, CA724 and CEA, confirming that cisplatin-based concurrent radiochemotherapy is more effective in reducing the tumor load.

The overactivation of proto-oncogene is the direct cause of malignant tumors, and its expression is highly consistent with the tumor malignancy[13]. DEK is a chromatin structure protein that can affect the DNA damage repair and susceptibility as well as cell apoptosis and senescence. At present, many studies have pointed out that the DEK gene is overexpressed in bladder cancer, breast cancer and other malignant tumors, which is the important reason for the malignant transformation and progress of tumor[14]. c-myc is the recognized cervical cancer-related proto-oncogene, and its
expression in cervical cancer tissue is significantly higher than that in adjacent normal tissue[15]. PIK3CA and its downstream signaling pathways can regulate the normal growth and apoptosis of cells, and their abnormal activation can lead to the evolution of cell cycle, inhibit apoptosis and increase angiogenesis. In the study, the above proto-oncogene expression in tumor tissue were compared between the two groups of patients before and after treatment, and it was found that compared with those before treatment, DEK, c-myc and PIK3CA mRNA expression in tumor tissue of both groups were lower after treatment; further compared with control group, observation group were with lower DEK, c-myc and PIK3CA mRNA expression in tumor tissue after treatment, and it shows that the cisplatin-based concurrent radiochemotherapy can more effectively inhibit the overexpression of proto-oncogene and reduce the malignant degree of tumor.

At the same time of the overexpression of proto-oncogene, the expression reduction and even deletion of tumor suppressor genes is another important cause of the malignant transformation of tumor cells. p53 is one of the genes most closely related to tumor, which can block the cycle of cells with abnormal DNA and induce its apoptosis, and also remove the various types of cells with carcinogenic tendencies[16]. SOCS-1 is a newly discovered tumor suppressor gene, and its methylation and loss of heterozygosity are important factors in the development of cervical cancer. In cervical cancer tissue, the probability of FHIT promoter methylation is as high as 40%, and its expression reduction plays an important role in the occurrence of multiple epithelial malignancies[17]. PTEN is a tumor suppressor gene that plays an important role in cell growth and development as well as apoptosis, and can negatively regulate PI3K pathway and make cell proliferation arrest in G1 phase to inhibit tumor cell proliferation. In the study, the above tumor suppressor gene expression in tumor tissues were compared between the two groups before and after treatment, and it was found that compared with those before treatment, tumor suppressor genes p53, SOCS-1, FHIT and PTEN mRNA expression in tumor tissue of both groups were higher after treatment; compared with those of control group, tumor suppressor genes p53, SOCS-1, FHIT and PTEN mRNA expression in tumor tissue of observation group were higher after treatment, confirming that cisplatin-based concurrent radiochemotherapy can be more effective in activating the expression of tumor suppressor genes and inhibiting tumor cell proliferation.

To sum up, it is concluded that cisplatin-based concurrent radiochemotherapy can significantly decrease the malignant degree of tumor, inhibit the excessive activation of proto-oncogene and increase the expression of tumor suppressor genes in patients with advanced cervical cancer, and it helps optimize patients’ condition and is expected to improve final treatment outcome.

References


