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Influence of sequential 125I particle chain implantation and transcatheter arterial chemoembolization on tumor cell killing effect in patients with liver cancer

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ABSTRACT

Objective: To study the influence of sequential ^{125}I particle chain implantation and transcatheter arterial chemoembolization (TACE) on tumor cell killing effect in patients with liver cancer. **Methods:** A total of 82 cases of patients with advanced liver cancer who were treated in our hospital between September 2014 and December 2016 were collected, reviewed and then divided into the control group (n=45) who received TACE alone and the observation group (n=37) who received sequential ^{125}I particle chain implantation and TACE. Serum levels of tumor markers, angiogenesis indexes and apoptosis molecules before and after treatments were compared between two groups of patients. **Results:** Before treatment, differences in serum levels of tumor markers, angiogenesis indexes and apoptosis molecules were not statistically significant between two groups of patients. After treatment, serum tumor markers AFP, CA199, CA153 and Ferritin levels in observation group were lower than those in control group; serum angiogenesis indexes VEGF, PEDF, ES and bFGF contents were lower than those in control group; serum apoptosis molecules p53 and Fas contents were higher than those in control group. **Conclusion:** Sequential ^{125}I particle chain implantation and TACE treatment of advanced liver cancer can effectively reduce tumor malignancy and promote tumor apoptosis.

1. Introduction

Transcatheter arterial chemoembolization (TACE) is currently the most common conservative treatment for patients with advanced liver cancer, and studies both at home and abroad have confirmed that the therapy can effectively kill local tumor cells[1,2]. But some studies have also shown that early recurrence is high after TACE treatment, and patients may need repeated treatment to ensure that the curative effect, which causes larger body pain and economic pressure to patients. Imaging-guided ^{125}I particle chain implantation has become a reliable therapy for patients with advanced malignant tumor, which produces constant killing effect on tumor cells via radiation in order to contain residual tumor cell proliferation and invasion, and reduce tumor recurrence rate[3,4]. In order to define the clinical significance of ^{125}I particle implantation therapy for patients with advanced liver cancer, ^{125}I particle chain implantation combined with TACE was used in the study, and its curative effect was discussed from tumor markers, angiogenesis indexes and apoptosis molecules, now reported as follows.

2. Information and methods

2.1 Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with primary liver cancer after pathological examination; (2) diagnosed for the first time, and not receiving systematic treatment before; (3) with estimated survival time 3 years. Exclusion criteria: (1) with history of ^{125}I particle treatment; (2) with malignant tumor diseases of other tissue organs; (3) combined with severe heart and kidney dysfunction; (4) associated with severe systemic infectious diseases.

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2.2 Case information

According to above inclusion and exclusion criteria, 82 cases of patients with advanced liver cancer who were treated in our hospital between September 2014 and December 2016 were selected as the research subjects, and patients themselves or their families signed the informed consent. The therapies were reviewed, and then the enrolled patients were divided into the control group (n=45) who received TACE alone and the observation group (n=37) who received sequential ^{125}I particle chain implantation and TACE. Thirty-seven patients were treated with a single TACE treatment in 45 patients with a ^{125}I chain. Control group included 25 men and 20 women that were 43-78 years old; observation group included 20 men and 17 women that were 40-76 years old. There was no significant difference in gender and age distribution between the two groups of patients (P>0.05) and the hospital ethics committee approved the study.

2.3 Therapy

Control group of patients received TACE treatment alone, specifically as follows: the chemotherapy drugs were pirarubicin (Shenzhen Main Luck Pharmaceutical Co., Ltd., approved by H10930105) 50 mg and cisplatin (Guizhou Hanfang Pharmaceutical Co., Ltd., approved by H20020273) 60 mg, and embolism agent iodized oil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., approved by H31021603) 5-25 mL. The specific dosage varied with the volume of tumor, blood supply, patient's surface area, and liver function and so on. The patients with rich blood supply received gelatin sponge (Jinling Pharmaceutical Co., Ltd., Nanjing Jinling Pharmaceutical factory, approved by H32024096) for embolism.

Observation group of patients received sequential ^{125}I particle chain implantation and TACE therapy, specifically as follows: ^{125}I particles were implanted in the liver tumors guided by ultrasound, the number of implantated particles and dosage should be based on the calculation results of radioactive particle implantation treatment planning system (TPS), and the average was 25 particles for each patient.

2.4 Observation indexes

Before treatment and 4 weeks after treatment, 5.0 mL fasting cubital venous blood was extracted from two groups of patients, anti-coagulated and centrifuged at low speed to take the upper serum and freeze it in low-temperature environment for test. Enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of tumor markers alpha fetoprotein (AFP), carbohydrate antigen 199 (CA199), carbohydrate antigen 153 (CA153) and Ferritin. RIA method was used to determine serum levels of angiogenesis indexes vascular endothelial growth factor (VEGF), pigment epithelium-derived factor (PEDF), endostatin (ES) and basic fibroblast factor (bFGF). ELISA was used to detect the contents of apoptosis molecules p53 and Fas in serum.

2.5 Statistical methods

Data were recorded and calculated by specially-assigned person and software was SPSS 21.0. Measurement data were in terms of mean ± standard deviation and comparison was by t test. Statistics P <0.05 was defined as statistical significance in differences.

3. Results

3.1 Tumor markers AFP, CA199, CA153 and Ferritin levels

Before treatment and 4 weeks after treatment, analysis of serum tumor markers AFP (ng/mL), CA199 (kU/L), CA153 (kU/L) and Ferritin (ng/mL) levels between two groups of patients was as follows: before treatment, serum AFP, CA199, CA153 and Ferritin levels were not significantly different between two groups of patients (P>0.05); compared with those before treatment, serum AFP, CA199, CA153 and Ferritin levels in both groups decreased significantly after treatment; compared with those in control group, serum AFP, CA199, CA153 and Ferritin levels in observation group decreased significantly after treatment (P<0.05).

Table 1.
Comparison of serum umor markers AFP, CA199, CA153 and Ferritin levels before and after treatment.

Groups	n	AFP		CA199		CA153		Ferritin	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	45	76.39±9.17	40.21±5.63*	113.28±17.94	68.21±7.59*	94.17±10.85	50.63±6.28*	731.38±90.66	394.26±40.55*
Observation group	37	76.28±9.05	21.65±3.09*	114.65±16.59	30.64±4.52*	93.68±9.74	27.34±3.41*	728.65±91.53	174.32±21.84*
t		0.218	18.293	0.176	29.387	0.176	17.28	0.159	23.173
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *P<0.05.

Table 2.
Comparison of serum angiogenesis indexes VEGF, PEDF, ES and bFGF contents before and after treatment.

Groups	*n*	VEGF		PEDF		ES		bFGF	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	45	265.38±34.71	89.26±9.15*	93.27±10.18	48.16±5.39*	176.29±20.54	104.37±13.85*	21.28±2.54	9.63±1.09*
Observation group	37	267.45±35.88	24.36±3.17*	92.35±10.94	17.53±2.19*	174.57±21.68	43.66±6.19*	21.19±2.78	2.75±0.38*
t		0.173	20.981	0.263	23.461	0.215	25.973	0.168	11.283
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

Table 3.
Comparison of serum p53 and Fas contents before and after treatment (pg/mL).

Groups	*n*	p53		Fas	
		Before treatment	After treatment	Before treatment	After treatment
Control group	45	4.05±0.48	5.17±0.64*	2.76±0.34	3.41±0.42*
Observation group	37	4.07±0.51	6.59±0.75*	2.74±0.35	5.03±0.56*
t		0.183	7.712	0.157	8.323
P		>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

3.2 Angiogenesis indexes VEGF, PEDF, ES and bFGF contents

Before treatment and 4 weeks after treatment, analysis of serum angiogenesis indexes VEGF (pg/mL), PEDF (μg/L), ES (ng/mL) and bFGF (pg/L) contents between two groups of patients was as follows: before treatment, serum VEGF, PEDF, ES and bFGF contents were not significantly different between two groups of patients ($P>0.05$); compared with those before treatment, serum VEGF, PEDF, ES and bFGF contents in both groups decreased significantly after treatment; compared with those in control group, serum VEGF, PEDF, ES and bFGF contents in observation group decreased significantly after treatment ($P<0.05$).

3.3 Apoptosis molecules p53 and Fas contents

Before treatment and 4 weeks after treatment, analysis of serum apoptosis molecules p53 and Fas contents between two groups of patients was as follows: before treatment, serum p53 and Fas contents were not significantly different between two groups of patients ($P>0.05$); compared with those before treatment, serum p53 and Fas contents in both groups increased significantly after treatment; compared with those in control group, serum p53 and Fas contents in observation group increased significantly after treatment ($P<0.05$).

4. Discussion

TACE has curative effect for treatment of advanced liver cancer, but there is the risk of early postoperative recurrence, and repeated TACE treatment can increase the patients′ trauma and economic pressures, so some scholars have recommended adding other auxiliary treatment in TACE treatment to expand the curative effect. Radioactive particle implantation is a reliable therapy for patients with advanced solid tumor, ^{125}I particle is the most widely used, and its short-range radiation has the following advantages: (1) penetration distance is only 1.7 cm, and the damage to normal tissue organs around the tumor is minimal[5]; (2) ray continues to kill tumor cells and inhibit tumor cell reproduction[6,7]; (3) radiation is not affected by respiratory movement; (4) continuous low-dose radiation can change the local immune state of the tumor and reduce its invasion ability[8]. In the study, ^{125}I particle chain implantation was added in the overall treatment of patients with advanced liver cancer. Tumor markers are the most common indicators that reflect the malignant degree of tumor, there are broad-spectrum tumor markers and specific tumor markers in serum of patients with advanced liver cancer, and their joint detection is with high sensitivity and specificity[9,10]. AFP and Ferritin are specific markers of liver cancer, and their serum contents are highly consistent with tumor malignancy[11]. CA199 and CA153 belong to the broad-spectrum markers and have been found to be highly expressive in malignant tumors such as colorectal cancer, cervical cancer and gastric cancer[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 AFP, CA199, CA153 and Ferritin contents in both groups of patients were lower after treatment; compared with control group, the observed group of patients were with lower serum AFP, CA199, CA153 and Ferritin levels after treatment. It confirms that adding ^{125}I particle chain implantation into the treatment can reduce the tumor malignancy effectively, which is speculated to be directly related to the continuous killing effect of the radiation after TACE.

There is strong angiogenesis in malignant tumors, it provides oxygen and nutrients for tumor cell proliferation and invasion, and there is the abnormally high expression of a variety of pro-angiogenesis factors in serum. VEGF is recognized as the strongest pro-angiogenesis factor, which is highly expressed in almost all malignant tumor tissues, and can activate multiple signaling pathways and induce the secretion of a lot of pro-angiogenesis factors[13,14]. PEDF belongs to the family of serine protease inhibitor, which has the functions such as nourishing nerve and

promoting angiogenesis. ES and bFGF are both downstream factors of VEGF, which can induce the increase of VEGF expression in the case of its high expression, and act on vascular endothelial cells and promote their proliferation and migration together with VEGF[15,16]. It was found in the study that compared with those before treatment, serum VEGF, PEDF, ES and bFGF contents in both groups decreased after treatment; further compared with control group, the observation group of patients were with lower serum VEGF, PEDF, ES and bFGF contents after treatment, confirming that sequential ^{125}I particle chain implantation and TACE can more effectively inhibit tumor angiogenesis, which is one of the important mechanisms for it to lower tumor malignancy.

The apoptosis activity of tumor cells directly determines their proliferation ability and malignant degree, and the apoptosis function is abnormal in patients with advanced hepatocellular carcinoma. p53 is a type of protein that triggers apoptosis, is a widely recognized tumor suppressor gene, and can block the cell cycle and directly induce cell apoptosis[17]. Fas belongs to tumor necrosis factor/ nerve growth factor receptor family, which can be combined with its receptor to positively promote apoptosis. In the study, serum levels of above apoptosis molecules were compared between two groups of patients before and after treatment, and it was found that compared with those before treatment, serum p53 and Fas contents in both groups of patients were higher after treatment; further compared with control group, the observation group of patients were with higher serum p53 and Fas contents after treatment, showing that sequential ^{125}I particle chain implantation and TACE can effectively activate the apoptosis pathway of tumor cells and promote the apoptosis of tumor cells.

It is thus clear that sequential ^{125}I particle chain implantation and TACE therapy for patients with advanced liver cancer is more effective than TACE therapy alone, it has the absolute superiority in inhibiting tumor malignancy and promoting tumor cell apoptosis, and it is worthy of popularization and application in clinical practice in the future.

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