

The effects of interventional therapy on serum HTATIP2/TIP30, B7-H4 and short-term curative effect in primary hepatocellular carcinoma

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Abstract. – OBJECTIVE: To explore the effects of interventional therapy on human immunodeficiency virus (HIV)-1 Tat interactive protein 2/Tat interactive protein 30 (HTATIP2/TIP30), B7-H4 and short-term curative effect in primary hepatocellular carcinoma.

PATIENTS AND METHODS: 62 patients with primary hepatocellular carcinoma admitted in our hospital from June 2015 to June 2016 were enrolled in this study and divided into observation group (n = 31) and control group (n = 31) according to the random number table. The patients in the control group were treated with radiofrequency ablation, and the patients in the observation group were treated with transcatheter arterial chemoembolization (TACE). The patients in both groups received liver protection therapy, hydration, antiemetic and stomach protection. The curative effects, the serum HTATIP2/TIP30, B7-H4, alanine aminotransferase (ALT) and total bilirubin in serum (TBIL), life quality before and after treatment, and survival during the 1-year follow-up, were compared.

RESULTS: The total short-term effective rate (70.97%) was higher than the control group (38.71%) ($p < 0.05$). The serum levels of HTATIP2/TIP30 and B7-H4 were decreased after treatment in both groups (observation group: $t = 17.1838$, 18.9795 , control group: $t = 8.3787$, 10.6393 , $p < 0.05$). The serum levels of HTATIP2/TIP30 and B7-H4 after treatment in the observation group were lower than the control group ($t = 12.2975$, 10.5361 , $p < 0.05$). The levels of ALT and TBIL were decreased after treatment (observation group: $t = 15.1716$, 34.5771 , control group: $t = 8.3374$, 17.3015 , $p < 0.05$). The levels of ALT and TBIL were lower in the observation groups than the control group ($t = 15.2697$, 16.8592 , $p < 0.05$). The improvement rate of life quality in the observation group (80.65%) was higher than the control group (54.84%) ($p < 0.05$). The survival rates of the two groups after 1-year follow-up were not statistically different ($p > 0.05$).

CONCLUSIONS: The short-term curative effect of interventional therapy of primary hepatocellular carcinoma is good. It can decrease serum HTATIP2/TIP30 and B7-H4, improves the liver function and the life quality of patients, prolonging the survival time. It has a high research value and it is worthy of further application.

Key Words:

Primary hepatocellular carcinoma, Interventional therapy, HTATIP2/TIP30, B7-H4, Short-term curative effect.

Introduction

Primary hepatocellular carcinoma (PHC) is a common malignant tumor, the modality and mortality of which are continuously increasing. It can significantly affect the physical and mental health and the safety of patients¹⁻⁴. It is difficult to diagnose the PHC at the onset and its progression is rapid. Furthermore, most PHC patients are complicated with hepatitis-liver cirrhosis history. Once there are significant clinical symptoms, the disease is already in middle or late stages, thus it's too late to carry out a surgery^{5,6}. Recently, with the development of therapeutic methods, as a main interventional therapy, transcatheter arterial chemoembolization (TACE) is the most mature, extensive, and accurate method in treating PHC⁷⁻⁹. It has been shown that HIV-1 Tat interactive protein 2/Tat interactive protein 30 (HTATIP2/TIP30) and B7-H4 are expressed in the hepatocellular carcinoma tissue and are closely related to the development of the tumor¹⁰⁻¹⁴. Thus, in this study, the effects of intervention-

al therapy on human immunodeficiency virus (HIV)-1 Tat interactive protein 2/Tat interactive protein 30 (HTATIP2/TIP30), B7-H4 and short-term effect in PHC were explored to provide a theoretical basis for the clinical treatment.

Patients and Methods

Patients

62 patients with PHC admitted in our hospital from June 2015 to June 2016 were enrolled in this study. All the patients were diagnosed based on the Criteria for the Clinical Diagnosis and Stage for Primary hepatocellular carcinoma¹⁵. The diagnostic methods included the clinical symptoms, physical signs, magnetic resonance imaging (MRI), computed tomography (CT), liver puncture and surgery. The patients were divided into observation group (n=31) and control group (n=31). In the observation group, there were 25 male patients and 6 female patients, the age was 30-72 years old and the average age was 51.32 ± 7.83 years old. The lesion location: 19 cases at right lobe, 9 cases at left lobe and 3 cases in both lobes. In the control group, there were 26 male patients and 5 female patients, the age was 32-75 years old and the average age was 50.83 ± 7.35 years old. The lesion location: 20 cases at right lobe, 8 cases at left lobe and 3 cases in both lobes.

Inclusion and Exclusion Criteria

Inclusion criteria: patients who were compliant to the criteria for PHC; a good mental state; an expected survival time longer than 3 months; patients who signed the informed consent. The study was approved by the Ethics Committee of our hospital.

Exclusion data: obstruction in the artery or vein in the liver; metastatic lesion other than the liver, with patients needed of liver transplantation; patients who were confirmed as cholangiocarcinoma type of PHC; patients that were complicated with severe abnormality such as lung, kidney or heart; mental disease; patients who had contraindication for interventional therapy.

Therapeutic Methods

Control Group

The patients were treated with radiofrequency ablation as follows: the patients were at the supine

position; after the application of local anesthesia, the preoperative imaging was used to select the puncture site, and then the puncture needle was used to penetrate into the liver tumor lesion with the guidance of ultrasound. The extremely cold radiofrequency therapy instrument was used for sequential radiofrequency therapy by adjusting the power and frequency.

Observation Group

The patients were treated with TACE based on the control group as follows: the patients were at supine position and routinely disinfected; after the application of local anesthesia, the femoral artery puncture was completed by modified Seldinger technique, the 5F catheter was implanted and 4.1F liver catheter was used for common hepatic artery radiography. The radiography of diaphragmatic artery, left gastric artery and superior mesenteric artery were also completed when necessary to confirm the tumor number, location, size, tumor thrombus in portal vein or hepatic vein or supplying vessels. If necessary, 3F micro-catheter was implanted to inject chemotherapy drug, and 10-20 mg Epirubicin or 0.25-0.5 g 5 FU and ultra-fluid lipiodol mixture were used to block the target vessels of the tumor, which was stopped when the local small portal vein was developed, or the iodized oil deposition of the tumor lesion became dense.

The patients in the both groups were treated by liver protection therapy, hydration, antiemetic and stomach protection.

The Evaluation Criteria of Short-Term Curative Effects

Complete improvement: the tumor lesion was gone and there was no new lesion.

Partial improvement: the total diameter of liver tumor lesion basement decreased $\geq 30\%$.

Stable: the total diameter of liver tumor lesion basement was decreased but didn't reach the partial improvement criteria.

Progression: the diameter of liver tumor lesion basement was increased $\geq 20\%$, or there were one or more new lesions.

Observation Indexes

The serum HTATIP2/TIP30 and B7-H4 in both group before and after treatment were observed, 5 mL peripheral venous blood were collected before and after the treatment, which were centrifuged with radius of 15 cm at 3000 r/min for 10 min to separate the serum. The samples

Table I. Comparison of short-term curative effects between two groups.

Group	Case number	Complete improvement (%)	Partial improvement (%)	Stable (%)	Progression (%)	Total effective rate (%)
Observation group	31	10 (32.26)	12 (38.71)	4 (12.90)	5 (16.13)	22 (70.97)
Control group	31	4 (12.90)	8 (25.81)	10 (23.26)	9 (29.03)	12 (38.71)
χ^2	—	—	—	—	—	6.5126
p	—	—	—	—	—	< 0.05

were preserved at -20°C for detection. HTATIP2/TIP30kits (Yingong Biological Technology Co., Ltd., Shanghai, China) and B7-H4 kit (Xitang Biological Technology Co., Ltd., Shanghai, China) were used to detect serum HTATIP2/TIP30 and B7-H4 strictly according to the instructions with Hitachi 7600 Automatic Biochemical Analyzer. The liver function indexes in the two groups before and after treatment were observed, and the above samples were used to detect alanine aminotransferase (ALT) and total bilirubin in serum (TBIL) with ALT and TBIL kits (Ikon Biological Technology Co., Ltd., Hangzhou, Zhejiang, China) strictly according to the instructions. The improvements of the life quality in both groups were observed according to Karnofsky Performance Status Scale (KPS): the score improved ≥ 10 points was defined as improved life quality; the score changed < 10 points was defined as stable life quality; the score reduced ≥ 10 points was defined as decreased life quality; the 1-year reoccurrence rate and survival rate in both groups were observed.

Statistical Analysis

SPSS 22.0 (IBM, Armonk, NY, USA) was used to analyze the data. The enumeration data were analyzed by χ^2 -test and the measurement data were analyzed by t -test. Data in the same group were compared by paired sample t -test and the data between groups were compared by independent-sample t -test. $p < 0.05$ was considered as statistically significant.

Results

Comparison of Short-Term Curative Effects between Two Groups

As shown in Table I, the total short-term effective rate (70.97%) was higher than the control group (38.71%) ($p < 0.05$).

Comparison of Serum HTATIP2/TIP30 and B7-H4 Before and After Treatment Between Two Groups

As shown in Table II, serum HTATIP2/TIP30 and B7-H4 were not statistically different between the two groups before treatment ($t = 0.6947$, 0.2148 , $p > 0.05$). The serum levels of HTATIP2/TIP30 and B7-H4 were decreased after treatment in both groups (observation group: $t = 17.1838$, 18.9795 , control group: $t = 8.3787$, 10.6393 , $p < 0.05$). The serum levels of HTATIP2/TIP30 and B7-H4 after treatment in the observation group were lower than the control group ($t = 12.2975$, 10.5361 , $p < 0.05$).

Comparison of Liver Functions Indexes Before and After Treatment Between Two Groups

As shown in Table III, levels of ALT and TBIL before treatment were not statistically different between two groups ($t = 0.1837$, 0.4964 , $p > 0.05$). The levels of ALT and TBIL were decreased after treatment in both groups (observation group: $t = 15.1716$, 34.5771 , control group: $t = 8.3374$, 17.3015 , $p < 0.05$). The levels of ALT and TBIL

Table II. Comparison of serum HTATIP2/TIP30 and B7-H4 before and after treatment between the two groups ($\bar{x} \pm s$).

Group		Case number	HTATIP2/TIP30 (ng/mL)	B7-H4 (μg/L)
Observation group	Before treatment	31	8.46 ± 1.37	48.97 ± 4.56
	After treatment	31	3.78 ± 0.65* [#]	30.94 ± 2.68* [#]
Control group	Before treatment	31	8.70 ± 1.35	49.21 ± 4.23
	After treatment	31	6.25 ± 0.91*	38.97 ± 3.29*

Note: $^*p < 0.05$ compared before treatment in within the same group; $^{**}p < 0.05$ compared with the control group after treatment.

Table III. Comparison of liver functions indexes before and after treatment between two groups ($\bar{x} \pm s$).

Group		Case number	ALT (U/L)	TBIL ($\mu\text{mol/L}$)
Observation group	Before treatment	31	117.94 $\pm$ 24.13	52.67 $\pm$ 3.25
	After treatment	31	49.83 $\pm$ 6.52 [#]	28.47 $\pm$ 2.15 [#]
Control group	Before treatment	31	119.03 $\pm$ 22.56	53.09 $\pm$ 3.41
	After treatment	31	82.18 $\pm$ 9.83 [*]	39.28 $\pm$ 2.85 [*]

Note: ^{*} $p < 0.05$ compared before treatment in within the same group; [#] $p < 0.05$ compared with the control group after treatment.

were lower in the observation groups than the control group decreased after treatment in both groups ($t = 15.2697, 16.8592, p < 0.05$).

Comparison of Life Quality Between Two Groups

As shown in Table IV, the improvement rate of life quality in the observation group (80.65%) was higher than the control group (54.84%) ($p < 0.05$).

Comparison of Survival Rate After 1-Year Follow Up

As shown in Table V, the survival rates of two groups after 1-year follow-up were not statistically different ($p > 0.05$).

Discussion

The development of PHC is usually on the basis of liver cirrhosis or progressive liver disease, thus the prognosis is poor. In the past, surgical excision and live transplantation were two widely accepted therapeutic methods specific for PHC^{4,16}. Due to huge difficulties and risks including transplantation recipient condition, donor source, perioperative recovery, surgery difficulty and postoperative long-term anti-rejection treatment, liver transplantation cannot be widely applied¹⁷⁻¹⁹. Surgical excision is the most widely applied method; however, it's limited by the requirements of indications, general condition,

tumor location, tumor size and liver function reserve^{20,21}. As the development of interventional therapy in the recent years, and as a minimally invasive surgery, it has several advantages such as less complications, good curative effect, less injury, less pain, economic and practical features. It can improve the immune function of body and the survival of patients, providing an opportunity for the PHC patients who are not eligible for the surgical excision. In the recent years, the interventional therapy for PHC is getting more and more attention, and it has been considered as the best non-surgical method for PHC. TACE is different from chemotherapy; in fact, the short-term curative effect of TACE is definite, which has been the favored method for the non-surgical treatment of PHC^{22,23}. The results in this study showed that the short-term total effective rate in the observation group was higher than the control group, indicating that TACE has a good short-term curative effect; the levels of ALT and TBIL in the observation group were lower than the control group after treatment, indicating that TACE can improve the liver function. The improvement rate of life quality in the observation group was higher than the control group, indicating that TACE can improve the life quality.

HTATIP2/TIP30 is a binding protein during the *in vitro* transcription of HIV, the molecule of which is 30000. As an adjuvant factor for HIV transcription, HTATIP2/TIP30 is widely expressed in some tumor tissues and human

Table IV. Comparison of life quality between two groups.

Group	Case number	Increased (%)	Stable (%)	Decreased (%)
Observation group	31	25 (80.65)	4 (12.90)	2 (6.45)
Control group	31	17 (54.84)	8 (25.81)	6 (19.35)
χ^2	—	4.7238	1.6533	1.2917
p	—	< 0.05	> 0.05	> 0.05

Table V. Comparison of survival rate after 1-year follow up.

Group	Case number	Survival rate (%)
Observation group	31	25 (80.65)
Control group	31	21 (67.74)
χ^2	–	1.3478
<i>p</i>	–	> 0.05

tissues. HTATIP2/TIP30 can interact with angiogenesis inhibitors and tyrosine kinase inhibitors in cell apoptosis and cell cycling, especially in the control of cell apoptosis and metastasis. Besides, HTATIP2/TIP30 can promote tumor metastasis by regulating angiogenesis related genes through binding with DNA or RNA polymerase II, cells proliferation and cell apoptosis^{24,25}. B7-H4 is a novel member of B7 family, which is highly expressed in various human tumors, and also closely related to the development of tumor. Furthermore, some researchers have shown that B7-H4 exists in the serum as a soluble form^{2,27}. It is reported that B7-H4 is related to tumor progression by inhibiting cytokine secretion, T cell proliferation, regulating T cell-mediated immune response and the expression in hepatocellular carcinoma. B7-H4 is derived from the tumor microenvironment or mesenchymal cells in tumor tissue. After the interventional therapy, there are apoptosis and necrosis of tumor cells; the tumor microenvironment is improved, so B7-H4 secretion is decreased, that's why the serum B7-H4 shows decreasing trend^{10,13,28-31}. The results in this study showed that serum HTATIP2/TIP30 and B7-H4 in the observation group were lower than the control group after treatment, indicating that interventional therapy for PHC can significantly decrease serum HTATIP2/TIP30 and B7-H4.

Conclusions

The short-term curative effect of interventional therapy of primary hepatocellular carcinoma is good. It can decrease serum HTATIP2/TIP30 and B7-H4, improves the liver function and the life quality of patients, prolonging the survival time. It has a high research value and it is worthy of further application. However, there are several limitations in this study, such as small sample size, short observation time and less observa-

tion indexes. Thus, in the future, a multi-sample and multicenter study and the observation time should be prolonged to provide a reliable basis for the clinical interventional therapy for PHC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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