Influence of gemcitabine thermal–chemotherapy infusion combined with carboplatin chemotherapy embolization on liver function, renal function and immune function in patients with primary carcinoma of liver

Bo Du, Peng Zhang

Department of Hepatobiliary Surgery, Chongqing People’s Hospital of KaiZhou District, Chongqing 405400, China

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Objective: To observe the influence of Gemcitabine Thermal-chemotherapy infusion combined with Carboplatin Chemotherapy embolization on liver function, renal function and immune function in patients with primary carcinoma of liver. Method: A total of 90 patients with primary carcinoma of liver in our hospital were selected and randomly divided into 2 groups: the control group (45 cases) and the observation group (45 cases). The patients in the observation group were treated by Gemcitabine Thermal-chemotherapy infusion combined with Carboplatin Chemotherapy embolization. And the patients in the control group were treated by Gemcitabine normal temperature chemotherapy infusion combined with Carboplatin Chemotherapy embolization. The changes of liver function, renal function and immune function were compared in 2 groups before and after treatment. Result: The comparison of ALT and AST in the two groups before treatment was not statistically significant. 3 d after treatment, the ALT and AST in both groups increased compared with that before treatment. And the ALT (175.35±10.06) U/L, AST (173.54±13.47) U/L, in control group were increased more significantly compared with ALT (84.21±12.07) U/L and AST (94.20±11.31) U/L in observation group. The difference was statistically significant. 30 d after treatment, The ALT and AST in both groups came back to the former level. The difference was not statistically significant. The comparison of BUN, Crea in the two groups before treatment, 3 d after treatment and 30 d after treatment were not statistically significant. The comparison of CD3+, CD4+, CD8+, CD4+/CD8+ and NK cells in the two groups before treatment were not statistically significant. 7 d after treatment, CD3+ (72.34±6.95), NK cells (23.56±6.62) increased compared with that before treatment. And they increased more significantly compared with CD3+ (64.78±5.46) and NK cells (18.32±5.72) in the control group. CD8+, (22.01±2.77) in observation group decreased more significantly compared with CD8+ (23.21±1.81) in control group. And the difference was statistically significant. Conclusion: Gemcitabine Thermal-chemotherapy infusion combined with Carboplatin Chemotherapy embolization has less damage to the liver function, no obvious influence to the renal function of patients with primary liver cancer. Also it can significantly improve the immune function.

1. Introduction

Primary liver cancer is a common malignant tumor in the world, with a high degree of malignancy, and the number of people who died of the disease every year is up to 696 thousand[1]. In our country, its mortality rate was also among the forefront. It has become an important public health problem which threat to human’s life and health[2-3]. The typical symptoms of patients with primary carcinoma of liver, such as fatigue, jaundice, liver area pain, often appeared in the middle-later period[4]. Most of patients have lost the best opportunity to surgery when they see a doctor[5]. Also, the operation made great damage to the liver tissue and the postoperative recurrence rate was also higher[6]. Therefore, chemotherapy as a non surgical treatment has gradually become an important treatment for primary liver cancer[7]. This study used Gemcitabine Thermal-
chemotherapy infusion combined with Carboplatin Chemotherapy embolization in the treatment of patients with primary liver cancer. Then, we observe its effect on the liver function, renal function and immune function, which provides scientific basis for further study on the treatment of primary liver cancer.

2. Materials and methods

2.1. General information

A total of 90 cases of patients with primary liver cancer in our hospital from June 2015 to June 2016 were selected as research objects. Selected requirements are as follows.

Inclusion criteria: (1) meet the diagnostic criteria of 'Standard Specification for diagnosis and treatment of primary liver cancer' (revised in 2011)[8]. And imaging examination and determination of tumor markers or pathological examination can make a definite diagnosis. (2) The result of liver function Child classification was A or B. (3) The maximum diameter of tumor was lower than 10cm, and the number of lesions was less than 5. (4) Expected survival time is not less than 6 months. (5) The patients had not previously received interventional therapy or surgery and other related treatment. (6) The patients had not taken drugs which would affect the immune function recently. (7) Informed consent had been signed.

Exclusion criteria: (1) With contraindication of interventional therapy. (2) With Intrahepatic and external metastasis or combined with tumor thrombus in portal vein and hepatic vein. (3) With severe heart, liver and kidney dysfunction. (4) With active gastrointestinal bleeding. (5) With other malignant tumors. The patients were randomly divided into 2 groups: 45 cases in the control group and 37 cases in the observation group. They were 30–76 years old. There are 39 males and 7 females in the observation group. They were 28–74 years old. There are 37 males and 8 females in the control group. They were 30–76 years old. Compared with the gender, age and other clinical data, we found no statistical difference.

2.2. Method

The observation group was treated by Gemcitabine Thermal-chemotherapy infusion combined with Carboplatin Chemotherapy embolization. Firstly, the catheter was placed into the feeding artery of tumors with the shadowgraph technique of arteriae hepatica communis. Then we dissolved the 1 000 mg/m² gemcitabine (produced by Jiangsu Hansoh Pharmaceutical Co., Ltd. Chinese medicine standard word: H20030104) into the 1 200 mL physiological saline. Then they were put into the heat therapy apparatus for thermal-chemotherapy infusion. The temperature at the entrance of the arterial catheter was set to 53°C, the velocity was set to 0.5–1.0 mL/s and the infusion time was set to 20–40 min. After these, 200 mg/m² gemcitabine and 200 mg/m² carboplatin (produced by Kunming GuiYan Pharmaceutical Co., Ltd. Chinese medicine standard word: H20053908) and 5–20 mL ultra fluid lipoid were mixed for hepatic arterial embolus. In the control group, 1 000 mg/m² gemcitabine in was dissolved into 1 200 mL physiological saline for hepatic arterial infusion under normal temperature. The other treatment was the same as the control group. Treat one time 30 d, continuous therapy for 3–4 times.

2.3. Observation indexes

The changes of the liver function (alanine aminotransferase ALT, aspartate aminotransferase AST) and renal function (blood urea nitrogen BUN, serum creatinine Crea) in patients were detected by auto clinical chemistry analyzer before treatment, 3 d after treatment and 30 d after treatment.

T lymphocyte subsets in peripheral blood of patients , mainly including CD3+, CD4+, CD8+, the ratio of CD4+/CD8+ and the counts of NK cells were detected by flow cytometer before treatment and 7 d after treatment.

2.4. Statistical Methods

SPSS 19.0 statistical package was conducted for statistical analysis. Measurement data were described as mean ± standard deviation with variance analysis, inter-group comparison was conducted by t test, inside group comparison was conducted by pair-matching t test, values of $P<0.05$ were considered to be statistically significant.

3. Results

3.1. Comparison of liver function in the two groups

The comparison of ALT and AST in the two groups before treatment were not statistically significant ($P>0.05$). 3 d after treatment, the ALT and AST in both groups increased compared with that before treatment. And the ALT (175.35±10.06) U/L, AST (173.54±13.47) U/L, in control group were increased more significantly compared with ALT (84.21±12.07) U/L and AST (94.20±11.31) U/L in observation group. The difference was statistically significant ($P<0.05$). 30 days after treatment, the ALT was (42.22±6.37) U/L, and AST was (45.15±1.23) U/L in observation group. The ALT was (40.05±5.33) U/L, and AST was (41.45±3.54) U/L in control group, which have came back to the former level. The difference were not statistically significant ($P>0.05$). See Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>Comparison of liver function in the two groups (n=45).</td>
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<tr>
<td>Groups</td>
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<tr>
<td>Observation</td>
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<td>Control</td>
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Compared with control group before treatment, $^aP<0.05$; compared with control group after treatment, $^bP<0.05$.

3.2. Comparison of renal function in the two groups

We analyzed the renal function indicators in the different time
before and after treatment. The results showed that the BUN before treatment, 3 d after treatment and 30 d after treatment were respectively (3.53±0.29) mmol/L, (3.61±0.31) mmol/L, (3.22±0.34) mmol/L; The Crea were respectively (46.34±13.62) μmol/L, (44.47±11.14) μmol/L, (48.12±12.45) μmol/L. The comparison of BUN, Crea in the two groups before treatment, 3 d after treatment and 30 d after treatment were not statistically significant (P>0.05). See Table 2.

### Table 2

Comparison of renal function in the two groups (n=45).

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>BUN (mmol/L)</th>
<th>Crea (μmol/L)</th>
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<tbody>
<tr>
<td>Observation</td>
<td>Before treatment</td>
<td>3.53±0.29</td>
<td>46.34±13.62</td>
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<tr>
<td></td>
<td>3 d after treatment</td>
<td>3.61±0.31</td>
<td>44.74±11.14</td>
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<td></td>
<td>30 d after treatment</td>
<td>3.22±0.34</td>
<td>48.12±12.45</td>
</tr>
<tr>
<td>Control</td>
<td>Before treatment</td>
<td>3.40±0.11</td>
<td>45.33±10.20</td>
</tr>
<tr>
<td></td>
<td>3 d after treatment</td>
<td>3.34±0.42</td>
<td>46.03±12.76</td>
</tr>
<tr>
<td></td>
<td>30 d after treatment</td>
<td>3.42±0.48</td>
<td>45.46±9.77</td>
</tr>
</tbody>
</table>

Compared with control group before treatment, \(^aP<0.05\); compared with control group after treatment, \(^bP<0.05\).

### 3.3. Comparison of immune function in the two groups

The comparison of CD3+, CD4+, CD8+, CD4+/CD8+ and NK cells in the two groups before treatment were not statistically significant (P>0.05). 7d after treatment, CD3+(72.34±6.95), NK cells (23.56±6.62) increased compared with that before treatment. And they increased more significantly compared with CD3+(64.78±5.46), and NK cells (18.32±5.72) in the control group. CD8+, (22.01±2.77) in observation group decreased more significantly compared with CD8+(23.21±1.81) in control group. And the difference was statistically significant (P<0.05). See Table 3.

### 4. Discussion

Primary liver cancer is a kind of malignancy caused by canceration of intrahepatic bile duct epithelial cells or hepatic cells. The disease spread throughout the world and the epidemic situation in China is very serious. The mortality rate is the second in the malignant tumors[2,3]. For the high degree of malignancy of primary liver cancer, the treatment of this disease has been the focus and difficulty in clinical work. Resection is an effective way to control the eradication of local lesions. However, resection can't completely solve the problem because of the great damage, high recurrence rate and low survival rate[9]. Therefore, chemotherapy as a non surgical treatment has gradually become an important treatment of primary liver cancer[7].

There are some studies showed that single treatment regimen can't control the progression of liver cancer[10]. Hepatic artery perfusion chemotherapy combined with embolization is commonly used in clinical treatment. This method can block the feeding artery of tumors, which makes apoptosis and necrosis of cancer cells. This administration route can also make the chemotherapy drugs maintaining a high concentration and a longer time in the local tissue, which makes the drugs more effectively killing the cancer cells[11,12]. In the recent years, hyperthermia as a new treatment method of malignancy, increasingly aroused people's wide attention. Hyperthermia combined with chemotherapy and embolization, can not only play the effect of interventional therapy, but also can induce the hypoxia and necrosis of cancer cells by using sensitivity of cancer cells to temperature. At present, this method has been widely used in the treatment of colorectal cancer, gastric cancer and other malignant tumors[13–15].

ALT, AST and BUN, Crea are important indicators of liver and kidney function[16,17]. The results of this study showed that the comparison of ALT and AST in the two groups before treatment were not statistically significant (P>0.05). 3 d after treatment, the ALT and AST in both groups increased compared with that before treatment. And the ALT (175.35±10.06) U/L, AST (173.54±13.47) U/L, in control group were increased more significantly compared with ALT (84.21±12.07) U/L and AST (94.20±11.31) U/L in observation group. The difference was statistically significant (P<0.05). 30 d after treatment, The ALT and AST in both groups came back to the former level. The difference were not statistically significant (P>0.05). The comparison of BUN, Crea in the two groups before treatment, 3 d after treatment and 30 d after treatment were not statistically significant (P>0.05). The results indicated that a liver injury existed in observation group and control group. However, compared with chemotherapy infusion combined with embolization at room temperature, thermal-chemotherapy infusion combined with embolization did little harm to liver function. The main reason may be that hot therapy increased membrane of cancer cells and vascular permeability by temperature. So, more chemotherapy drugs and iodized oil entered into cancer cells, which made the drugs into the normal liver cells decreased[18]. Therefore, the liver function of patients received hot therapy damaged little. And the two methods didn't affect the renal function.

A number of studies have shown that patients with primary liver cancer appeared immune function inhibition. Specifically, CD3+, CD4+, CD4+/CD8+ and NK cell counts significantly decreased and CD8+ significantly increased. And the immune function plays...
an important role in enhancing the patient’s treatment effect[19-21].
The result showed that the comparison of CD3+ and CD4+, CD8+, CD4+/CD8+ and NK cells in the two groups before treatment were not statistically significant (P>0.05). 7 d after treatment, CD3+ (72.34±6.95), NK cells (23.56±6.62) increased compared with that before treatment. And they increased more significantly compared with CD3+ (64.78±5.46) and NK cells (18.32±5.72) in the control group. CD8+ (22.01±2.77) in observation group decreased more significantly compared with CD8+ (23.21±1.81) in control group. And the difference was statistically significant (P<0.05). The result showed that compared with chemotherapy infusion combined with embolization at room temperature, thermal-chemotherapy infusion combined with embolization can improve the immune function of the patients effectively. Gemcitabine, a new anticancer drug, can block the cell cycle from G1 phase to S phase, inhibit angiogenesis, such as VEGF, which cubes the cancer cell proliferation process and inhibits the angiogenesis of tumor. And then, the immune function is improved[22]. The effective rate of gemcitabine arterial chemotherapy in normal temperature is lower than that in a high temperature[23]. Therefore, thermal-chemotherapy infusion helps to play the efficacy of gemcitabine and improve the immune function.

Gemcitabine Thermal-chemotherapy infusion combined with Carboplatin Chemotherapy embolization has less damage to the liver function, no obvious influence to the renal function of patients with primary liver cancer. Also it can significantly improve the immune function. It is worthy of popularization and application in clinical treatment.

References