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Safety of implanting sustained-release 5-fluorouracil into hepatic cross-section and omentum majus after primary liver cancer resection

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Abstract

This study was designed to evaluate the short-term safety of implanting sustained-release 5-fluorouracil (5-FU) into hepatic cross-section and omentum majus after primary liver cancer resection and its impact on related indexes of liver. Forty patients were selected and divided into an implantation group (n = 20) and a control group (n = 20). On the first day after admission, first week after surgery, and first month after surgery, fasting venous blood was extracted from patients for measuring hematological indexes. The reduction rate of alpha fetoprotein (AFP) on the first week and first month after surgery was calculated, and moreover, drainage volume of the abdominal cavity drainage tube, length of stay after surgery, and wound healing condition were recorded. We found that levels of alanine aminotransferase, aspartate amino transferase, blood urea nitrogen, creatinine, total bilirubin, albumin, and white blood cells measured on the first week and first month after surgery, length of stay, and wound healing of patients in the two groups had no significant difference ($P > 0.05$). Drainage volume and reduction rate of AFP of two groups were significantly different on the first week and first month after surgery ($P < 0.05$). Implanting sustained-release 5-FU into hepatic cross-section and omentum majus after primary liver cancer resection is proved to be safe as it has little impact on related indexes.

Keywords

fluorouracil, primary liver cancer, safety

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Introduction

Primary liver cancer whose global incidence rate ranks seventh and whose death rate ranks fourth is one of the most commonly seen malignant tumors worldwide. In China, primary liver cancer has an incidence rate of 25.7 per 100,000, secondary to lung cancer and gastric carcinoma.[1] Hepatocellular carcinoma, the most common liver carcinoma, accounts for 75% of primary liver carcinoma. Hepatocellular carcinoma can promote formation of other structures in liver such as bile duct, vessels, and immune cells. There are various causes for hepatocellular carcinoma worldwide; HBV infection, however, is the major cause in China / for Chinese liver cancer patients. Most cases turn to develop hepatocellular carcinoma after experiencing cholesterol and hepatocirrhosis.[2]

5-FU as a kind of broad spectrum anti-tumor drug[3] intervenes metabolism of nucleic acid of tumor cells through multiple approaches and

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metabolites.[4] 5-FU as a commonly used metabolic anti-tumor drug clinically is able to produce more toxic and side effects and rapidly decrease blood concentration if being administrated in a large dose.[5] To solve such problems, studies on sustained-release 5-FU have been carried out. Haiping et al.[6] found that regional treatment with sustained-release 5-FU could improve the killing effect of chemotherapeutics on tumor cells, which was helpful to prevent local recurrence and distant metastasis of tumor and make up defects of systemic administration. Moreover, Yuanyuan et al.[7] found that local implantation of sustained-release 5-FU could obviously lower serum alpha fetoprotein (AFP) level and early recurrence rate of liver cancer.

By comparing the postoperative situation/indexes of patients with and without implantation of slow-released 5-FU after primary liver cancer resection, this study discussed the safety of sustained-release 5-FU implantation and its influence on related indexes.

Materials and methods

General data

Forty patients with primary liver cancer who underwent surgical resection in the department of hepatobiliary surgery of Huaihe Hospital of Henan University, Kaifeng, Henan, China, from March 2012 to March 2014 were selected as research objects. They were divided into an implantation group (implantation of sustained-release 5-FU into hepatic cross-section and omentum majus after surgical resection) and a control group (surgical resection only), with 20 cases in each group.

The following patients were included in the study: those who were classified as either stage I or II by TNM classification criteria formulated by Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) in 2003; those who were pathologically confirmed with primary liver cancer; those who were determined with Child classification level A or B liver function; those who had undergone surgery operated by the same operation group; and those who had no organic diseases in important organs such as the heart, lungs, brain, and kidney. The following patients were excluded: those who had undergone chemotherapy, radiotherapy, or interventional therapy before surgery; those who had other liver diseases (except hepatitis B); and those who had undergone non-radical resection.

Methods

Preparation before and after surgical resection. Patients were found with pain or discomfort in the upper abdomen as well as weight reduction and some even showed symptoms such as nausea, emesis, and anorexia. All patients were confirmed with primary liver cancer by B ultrasonography, enhanced computed tomography (CT), and/or contrast-enhanced magnetic resonance carried out on the abdomen before surgery. Also, detection of blood indexes, biochemical indexes and AFP, infusion, and examination of the heart and lungs were performed on the first day after admission.

After surgery, continuous electrocardiogram monitoring, gastrointestinal decompression, and retention catheterization as well as acid suppression treatment, anti-inflammation treatment, liver protection treatment, and total parenteral nutrition support were carried out. In addition, the drainage volume of the peritoneal cavity drainage tube was recorded. In the morning of the first, third, and fifth day after surgery, blood and biochemical examinations were performed. Medication of antibiotics and liver-protection drugs stopped according to concrete conditions. The urinary catheter was removed on the first day after surgery. The drug was replaced on the first day and then replaced every 2 or 3 days. The drainage tube was taken away when liquids flew out. Patients were asked to take a liquid diet first, followed by a semi-liquid diet and a normal diet after gas release. On the seventh day after surgery, blood routine examination, biochemical test, and AFP detection were performed once again. Patients left the hospital after sutures were removed during days 7–9 after surgery.

Specific observation index. General data of patients included gender, age, and size and location of tumor.

Related items and indexes which needed to be detected and recorded before and after surgery were as follows. On the first day after admission, first week after surgery, and first month after surgery, fasting venous blood was extracted from patients for measuring white blood cells (WBC), creatinine (Cr), blood urea nitrogen (BUN),

alanine aminotransferase (ALT), aspartate amino transferase (AST), total bilirubin (TB), albumin (ALB), and alpha fetoprotein (AFP). The reduction rate of AFP on the first week and first month after surgery was calculated. Drainage volume, length of stay after surgery, wound healing condition, and adverse reactions were also recorded.

Therapeutic method. Patients in both groups underwent one-stage resection of liver cancer. After washing of the abdominal cavity and before close of the abdominal cavity, 300 mg of 5-FU implants (trade name: Sinofuan, Wuhu Simcere Pharmaceutical Co., Ltd., batch no.: 20091015) were evenly spread over the liver section; the liver section was then sutured. Moreover, 300 mg of 5-Fu implants were evenly spread at the root of mesentery of omentum majus in the adnominal cavity; omentum majus was sutured after embedment. Patients in the control group were given no measures at the end of the surgery; the abnominal cavity was directly closed. After surgery, patients in both groups were given the same postoperative adjuvant therapy and rehabilitation nursing.

Statistical method

All statistical data were analyzed and processed by SPSS17.0. Measurement data were processed by t-test and enumeration data were by chi-square test. $P < 0.05$ means the difference was statistically significant.

Results

Comparison of general data of the implantation and control groups before surgery

Gender, age, and size and location of lesions were compared between the two groups. Gender, average age, and size and location of tumor measured by abdominal ultrasonography, abdominal CT, and/or MRI were of no significant difference between the two groups ($P > 0.05$). In the implantation group, the diameters of lesions in four patients were smaller than 3 cm, the diameters of lesions in 11 patients were in the range of 3–5 cm, and the diameters of lesions in five patients were larger than 5 cm. In the control group, the diameters of lesions in two patients were smaller than 3 cm, the diameters of lesions in 10 patients were in the range of 3–5 cm, and the diameter of lesions in eight patients were larger than 5 cm. In the implantation group, there were 11 cases of left-lobe liver cancer and nine cases of right-lobe liver cancer; in the control group, there were six cases of left-lobe liver cancer and 14 cases of right-lobe liver cancer. It indicated that the results of the two groups were comparable.

Comparison of hematological indexes between two groups

In the morning of the first day after admission, blood indexes, biochemical indexes, and tumor marker of fasting blood were detected. By comparison, we found that the difference of WBC, Cr, BUN, ALT, AST, TB, ALB, and AFP levels between the two groups showed no statistical significance (Table 1); hence, the results of two groups were comparable.

In the first week and first month after surgery, WBC of fasting blood was measured. The WBC level measured at different time points in the two groups showed no significant difference ($P > 0.05$, Table 1) and the comparison results of Cr, BUN, ALT, AST, TB, and ALB were the same as that of WBC ($P > 0.05$). AFP level reduced after surgery was compared to before surgery; and the reduction rate of AFP level of two groups at different time points was compared and the difference had statistical significance ($P < 0.05$).

Comparison of postoperative conditions between two groups

Table 2 shows that adverse reactions took place in both groups, but the difference had no statistical significance ($P > 0.05$). After surgery, the drainage volume of peritoneal cavity drainage tube (until the tube was removed) in the two groups was recorded and compared and the difference had statistical significance ($P < 0.05$). Additionally, the difference of length of stay (from the first day after surgery to the discharge day) between the two groups showed no statistical significance ($P > 0.05$). Moreover, wound healing of patients in the two groups was recorded and compared after surgery, and the difference also had no statistical significance ($P > 0.05$).

Table 2 suggested that the total drainage volume of abdominal cavity drainage tube had no remarkable difference between two groups ($P > 0.05$). Drainage volume significantly increased after 5-FU was implanted. The reason might be 5-FU

Table 1. Comparison of hematological indexes between the two groups.

Index		Implantation group (n = 20)	Control group (n = 20)	Statistics t	*P* value
WBC (*10~9/L)	Before surgery	5.08 ± 1.96	4.75 ± 1.46	0.5965	>0.05
	One week after surgery	8.88 ± 2.88	7.28 ± 2.38	1.9568	>0.05
	One month after surgery	4.78 ± 1.298	4.33 ± 0.96	1.6949	>0.05
Cr (μmol/L)	Before surgery	74.78 ± 12.98	74.18 ± 13.58	0.1415	>0.05
	One week after surgery	66.46 ± 14.01	59.85 ± 13.44	1.5214	>0.05
	One month after surgery	71.77 ± 11.72	65.78 ± 9.56	1.7716	>0.05
BUN (mmol/L)	Before surgery	4.63 ± 1.26	5.33 ± 1.57	1.5486	>0.05
	One week after surgery	4.85 ± 1.51	4.91 ± 2.11	0.0664	>0.05
	One month after surgery	4.45 ± 1.12	4.82 ± 1.39	1.0016	>0.05
ALT (U/L)	Before surgery	37.21 ± 13.98	28.79 ± 13.48	1.9386	>0.05
	One week after surgery	91.98 ± 49.98	97.34 ± 58.66	0.3122	>0.05
	One month after surgery	37.81 ± 19.85	36.22 ± 15.74	0.2805	>0.05
AST (U/L)	Before surgery	40.62 ± 21.05	30.09 ± 12.07	1.9432	>0.05
	One week after surgery	37.79 ± 14.68	51.64 ± 76.39	0.7984	>0.05
	One month after surgery	33.41 ± 11.25	27.18 ± 9.14	1.9167	>0.05
TB (μmol/L)	Before surgery	19.03 ± 10.56	13.76 ± 6.09	1.9353	>0.05
	One week after surgery	28.71 ± 11.89	22.01 ± 14.05	1.6308	>0.05
	One month after surgery	14.49 ± 4.86	13.63 ± 4.06	0.6063	>0.05
ALB (g/L)	Before surgery	38.38 ± 3.78	37.69 ± 2.98	0.6737	>0.05
	One week after surgery	33.72 ± 2.48	31.61 ± 4.45	1.8679	>0.05
	One month after surgery	37.36 ± 4.11	37.48 ± 4.36	0.0908	>0.05
AFP (ng/mL)	Before surgery	404.88 ± 117.79	434.84 ± 127.47	0.7725	>0.05
AFP reduction rate	One week after surgery	84.41% ± 8.18%	78.59% ± 6.61%	2.4903	<0.05
	One month after surgery	93.56% ± 4.29%	89.26% ± 6.15%	2.5544	<0.05
Preoperative Child grade (n)	Grade A	8	14	0.6832	>0.05
	Grade B	12	6		

Table 2. Comparison of untoward reactions, drainage volume of peritoneal cavity drainage tube, length of stay, and wound healing of patients in two groups after surgery.

Index	Implantation group (n = 20)	Control group (n = 20)	Statistics t	*P* value
Abdominal pain (n)	6	4	0.5272	>0.05
Ascites (n)	9	10	0.4023	>0.05
Intra-abdominal infection (n)	3	4	0.3958	>0.05
Intra-abdominal hemorrhage (n)	0	0	–	–
Bile leakage (n)	1	0	0.2153	>0.05
Drainage volume (mL)	1186.12 ± 201.55	1057.54 ± 177.56	2.1395	<0.05
Length of stay (d)	8.67 ± 1.84	9.67 ± 4.84 3	0.9086	>0.05
II/class A	19	19	0.5261	>0.05
II/class B	1	1		

induced local inflammatory reaction and thus increased abdominal effusion, or local concentration of chemotherapeutics produced chemical stimulus on peritoneum[8] and thus increased reactive abdominal effusion.

Discussion

Sustained-release 5-FU can release 5-FU slowly and stably and sustain it at a high level; besides, because of the low concentration of drug in peripheral blood, the action time of 5-FU on the tumor is prolonged, tumor cells can be effectively killed or inhibited, and toxic and side effects throughout the whole body can be reduced.[9]

The current study revealed that implantation of sustained-release 5-FU had no obvious influence on levels of WBC, Cr, BUN, ALT, AST, TB, and ALB and the drug produced low toxicity in the blood system, renal function, and liver function.

The research results suggested the safety of 5-FU was in close correlation to the action mechanism and administration mode of 5-FU. 5-FU is embedded in high molecule polymerization material skeleton in the form of a micro-capsule. The drug released from the micro-capsule is passively transported outside the skeleton through penetrative diffusion and then it reaches target positions. Slow diffusion will result in a concentration of small dose and low concentration of the drug on target spots, which reduces toxic and side effects produced by 5-FU. Moreover, after the implantation, released 5-FU plays relevant functions after diffusing into extracellular tissue fluid; the extremely small amount of the drug entering into the blood through the capillary wall results in low peak concentration, which avoids toxic and side effects.[10–13]

We found that sustained-release 5-FU could inhibit liver cancer and rapid proliferation of residual cancer cells after surgical resection, and sustained-release 5-FU conforming to the concept and requirement of regional chemotherapy and interstitial chemotherapy was operable and valuable.

For patients with primary liver cancer, sustained-release 5-FU implanted after surgical resection has been proved to have no obvious influence on levels of WBC, transaminase, TB, Cr, BUN, ALB, and AFP and have no impact on length of hospital stay and wound healing, though drainage volume of abdominal cavity drainage tube increased; hence sustained-release 5-FU is safe. A significant reduction rate of AFP of the implantation group suggested that sustained-release 5-FU could restrain rapid proliferation of residual cancer and intrahepatic metastasis in the short term after surgery. But studies with a large sample size and long follow-up period need to be carried out to explore whether sustained-release 5-FU is effective in lowering recurrence rate and metastasis rate of liver cancer and improving survival rate.

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