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ORIGINAL ARTICLE

Clinical research on ultrasonically guided intrahepatic injections of HAS in interventional treatment of liver carcinomas

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Summary

Purpose: *To study the clinical value of intrahepatic injections of Highly Agglutinative Staphylococcin (HAS) in the interventional treatment of liver carcinomas.*

Methods: *Under ultrasonic guidance, intrahepatic injections of HAS were administered in 22 cases of pathologically diagnosed liver carcinomas, 3 days, 7 days, 30 days, 3 months, 6 months, 9 months, and 12 months after microwave coagulation therapy. The dose of each injection was 2000U.*

Results: *Immunohistochemical staining of the sample from the tumor site after HAS administrations demonstrated a significant increase in the number of antitumor immune cells compared with that before the injections ($p<0.01$) and an improvement in local immune status. One-year survival rate and recurrence rate, which were determined by Kaplan-Meier method, were 93.8% and 81.9% respectively.*

Conclusions: *As a new route of administration, intrahepatic injections of HAS are a safe and effective procedure and deserves further clinical research and discussion.*

Key words: *Highly Agglutinative Staphylococcin (HAS), interventional treatment, liver cancer, ultrasonic guidance*

Introduction

At present, it is believed that a decline in immune function is the main cause of tumor development [1,2]. Since antitumor immunity mainly relates to cell-mediated immunity, how to strengthen cell-mediated immunity to kill tumor cells has become a hot topic of oncotherapy research [3-5]. Therefore, we selected HAS, a representative of cellular immunopotentiator agent of superantigen class, and applied it as interventional treatment for liver carcinomas by means of ultrasonic guidance. The purpose of the present study was to investigate the clinical value of HAS on liver carcinomas.

Methods

Clinicopathological data

From December 1999 to February 2001, ultrasonically guided intrahepatic injections of HAS were administered to 28 nodules of 22 patients diagnosed with carcinomas in the liver , of whom, 19 had hepatocellular carcinomas (HCC), 3 metastatic carcinomas (2 primary gastric carcinomas, and 1 rectal carcinoma); 9 patients had poorly differentiated carcinomas, 11 moderately differentiated carcinomas and 2 well-differentiated carcinomas (Table 1). The mean maximum diameter of the tumors was 3.8±1.2 cm (range 1.7-5.5) among which 8 were less than 3cm, 9 from 3 to 5cm and 5 more than

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Table 1. Disease data of the enrolled participants

	Primary (HCC)	*Metastatic*		*Grade of differentiation*		
		Gastric carcinoma	*Rectal carcinoma*	*Poorly differentiated*	*Moderately differentiated*	*Well differentiated*
Number of patients	19	2	1	9	11	2

HCC: hepatocellular carcinoma

5cm. There were 16 cases (73.0%) with a solitary nodule and 6 cases (27%) with multiple nodules All of the cases had received ultrasonically guided percutaneous microwave coagulation therapy before intrahepatic injections of HAS. After microwave treatment, coagulative necrosis of the tumors was determined by biopsy.

Clinical methods

Before HAS intrahepatic injections, HAS was administered mintramuscularly for 3 days, at a dosage of 500U on the 1st day, 1000U on the 2nd day and 2000U on the 3rd day, given once a day. After administration, body temperature was monitored three times a day and the patient was observed for local and systematic adverse reactions. After it was confirmed that the patient had no allergic reaction, ultrasonically guided intrahepatic injections of HAS were given at seven time points, namely the 3rd, 7th and 30th days and the 3rd, 6th, 9th and 12th months, at a dosage of 2000U. Before each injection, biopsy was taken from the tumor site, fixed by formalin and embedded in paraffin to prepare H&E staining paraffin sections, and then regular pathological study of the sections was made. Meanwhile, specific immunohistochemical staining was performed on the sections to observe the immune response of the sample from the tumor site. After HAS injection, monitoring was conducted to detect body temperature and side effects. The examinations of liver and kidney functions and alpha-fetoprotein (AFP), blood and routine urine test , ECG, color Doppler ultrasonography of the abdomen and post-contrast CT scan were performed before and after the injection. Follow-up started from the first administration and ended in February 2001. During the treatment period, no other anticancer therapy was given.

Statistics

SAS software was applied for statistical analysis of data. Student's t-test was used to compare the conditions before and after treatment, and Kaplan-Meier method with log rank test to estimate survival and recurrence rate. A two-sided p value <0.05 was considered as statistically significant.

Results

Clinical follow-up

The follow-up of the 22 patients lasted from 2 to 14 months (mean 9.8±2.9). Of all the patients, only one (with HCC) (4.5%) died of massive hemorrhage of the upper digestive tract 10 months after treatment. This patient had no local recurrence or distant metastasis . Among the 21 survivors, 4 had recurrence (18.2%), including 3 with HCC having local recurrence 2, 3 and 8 months after treatment respectively and 1 (hepatic metastasis) having distant metastasis 1 month after treatment. The HCC patients tended to have lower recurrence rate and later recurrence compared with those with hepatic metastasis. The patients with recurrence were given ultrasonically guided percutaneous microwave coagulation therapy again, followed by further intrahepatic injection of HAS, and survived for nearly 10 months (9.9±3.6) .

Imaging examinations

2D ultrasonography and CT scan showed that the tumor foci reduced from pre-treatment 1.7 to 5.5cm to post-treatment 1.5 to 4.0cm, a reduction rate of 28.0%. No clear blood flow signal was detected in recurrent foci by color Doppler flow imaging (CDFI) and no enhancement was found by post-contrast CT scan. CDFI for 4 patients with recurrence showed intratumoral artery-like blood flow signal with enhancement demonstrated in post-contrast CT scan, but after microwave coagulation therapy followed by further injection of HAS , no abnormality was found by the CDFI and post-contrast CT scan during follow-up.

Biopsy of tumor site

For all the patients during the follow-up , a re-biopsy of multiple points at the tumor site was performed, in which regular H&E staining showed coagulative necrotic tissue and fibrous tissue proliferation, accompanied by different degrees of immune cell infiltration, without carcinoma. Immunohistochemical staining showed that after treatment, the immune cells infiltrating the tumor and liver tissue were mainly CD+3 , CD+56 and CD+68 cells. The antitumor immune cells at the tumor site significantly increased compared to

those before treatment (p<0.01) and local cell-mediated immunity was improved.

Reactions after treatment

All patients showed obvious reactions on the date HAS was injected locally, mainly fever, with body temperature of 37.5 to 41.0°C, (mean 38.8±0.5°C), of 1- 3 day(s) duration. For some patients, symptoms like different degrees of muscle pain and weakness were noticed, without other obvious discomfort. The body temperature returned to normal without special measures and all the above symptoms disappeared 3 days after discontinuation of administration. No complication were encountered during treatment. No liver or kidney damage was noticed, blood and routine urine test and ECG showed no abnormality, the level of serum AFP significantly declined or became normal. One patient with extensive redness , swelling and induration at the site of intramuscular injection, accompanied by local pruritus, possibly of allergic origin, was excluded from further analysis.

Discussion

HAS is a bio-activator that is extracted from staphylococcus aureus culture with high agglutination titer. As a new antitumor biological response modifier, it has a wide spectrum of biological activities. Being the first super antigen antitumor biologic [2,3] applied in domestic and foreign clinical practice, it has been primarily applied to tumor treatment with obvious antitumor immunological treatment effect. So far, however, the clinical application of HAS to the treatment of liver carcinomas has been mostly limited to systematic immune supportive treatment such as intravenous infusion, intramuscular injection and oral administration [4-6], and as the drug concentration is reduced when it reaches the tumor location through systematic circulation and metabolism, its effects are affected, therefore, the popularization and use of HAS for the treatment of liver carcinomas is limited [7-10]. Previous evidence has demonstrated the effects of HAS at a large dosage by chemotherapy on liver carcinomas. However, this therapy was only applicable to palliative immune supportive treatment [11,12] at the time of transcatheter arterial chemoembolization for middle-advanced stage liver carcinomas. The clinical data of the 22 patients in this group with intrahepatic injection treatment of liver carcinomas have shown its superiority that is absent from traditional systemic administration and the administration by chemotherapy pump via hepatic artery. Intrahepatic injection in combination with microwave coagulation therapy prevents the reduction in local drug concentration due to systemic administration, but also adverse reactions such as reduction in white blood cells caused by chemotherapy drugs administered by chemotherapy pump via hepatic artery.

Conflict of interests

The authors declare no confict of interests.

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