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# Controlled prospective evaluation of Sho-saiko-to in prevention of hepatocellular carcinoma in patients with cirrhosis of the liver

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**Abstract**

Sho-saiko-to (Xiao-Chai-Hu-Tang), a traditional Oriental medicine with antitumor effects in experimental animals and beneficial effects in cirrhosis of the liver was examined. A controlled prospective study was done to evaluate the usefulness of Sho-saiko-to in the prevention of hepatocellular carcinoma (HCC). Pairs of subjects from a group of 260 patients with cirrhosis were matched for age, sex, presence of HBs antigen, and the severity of liver dysfunction. Each patient was randomly assigned to receive either conventional medicine (control group) or 7.5 g of Sho-saiko-to daily in addition to the conventional medicine (trial group). The patients were monitored during up to 34 months of treatment, and the incidence of HCC in the two groups were compared. Twenty-one patients in the control group and 12 patients in the trial group were found to have HCC. To rule out HCC already present in considerable size at the time of entry into this study, the patients found to have HCC within the first 6 months were not counted. There remained 17 patients in the control group and 9 in the trial group found to have HCC ; the difference was significant. Sho-saiko-to may prevent or delay the emergence of latent HCC in patients with cirrhosis of the liver.

**Key words** Sho-saiko-to (Syô-saiko-tô), hepatocellular carcinoma, cirrhosis of the liver, prevention.

**Abbreviations** AFP, $\alpha$-fetoprotein ; HCC, hepatocellular carcinoma ; US, ultrasonography ; Sho-saiko-to (Xiao-Chai-Hu-Tang), 小柴胡湯.

## Introduction

Hepatocellular carcinoma (HCC) almost always arises from chronic liver disease ; cirrhosis of the liver is present in 80－90% of patients found to have HCC in Japan.[1] We have reported the results of a three year prospective study involving 160 patients with cirrhosis of the liver,[2] in which the serum $\alpha$-fetoprotein (AFP) level was assayed every two months and ultrasonography (US) was conducted every three months. Twenty-four patients were found to have HCC during this 3-year study, in which the cumulative incidence was 23%. Here, Sho-saiko-to, a traditional Oriental medicine with immunomodulatory[3] and antitumor[4-6] effects, was investigated to find if it was useful for the prevention of HCC.

## Subjects and Methods

*Patients* : During the 34 months beginning in June 1985 and ending in April 1988, 260 patients

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with cirrhosis of the liver (diagnosed clinically or pathologically) from whom consent was obtained, were studied in six hospitals. The protocol was approved by the Ethical Committee on Human Investigations of each hospital. On entry into the study, the subjects were examined by ultrasound (US) to rule out HCC. The patients all had an AFP titer lower than 200 ng/ml within the 3 months before entry. Pairs of patients were matched for age, sex, presence of HBs antigen (Table I), and scores of the severity of liver dysfunction based on the levels of serum albumin, cholinesterase and bilirubin (Table II). One patient from each pair was randomly assigned to the trial group and the other to the control group. The patients in the control group were administered conventional medicine, and the patients in the trial group were given Sho-saiko-to (Tsumura & Co., Tokyo) at a daily dose of 7.5 g *per os* in addition to the conventional medicine. All patients were prospectively monitored every 2 months by AFP assay and every 3 months by US.

*Methods* : US was conducted with high-resolution linear-array and convex-array real-time scanners (3.5 MHz, model EUB 340 and 40, Hitachi Medical Corp. ; model SSD 280 and 256, Aloka Co., Ltd. ; and model SSA 90A, Toshiba Systems Co., Ltd. ; Japan). Selective hepatic arteriography and computed tomography (CT) were performed if HCC was suspected. An US-guided biopsy was conducted for confirmation of the diagnosis of HCC when indicated. Statistical analysis was done by the log-rank test, generalized Wilcoxon test, likelihood ratio test, Z-test, and *t*-test. To rule out cases of HCC already present in considerable size at the time of entry into this study, additional analysis was done for only these patients found to have HCC at least 6 months after the start of the study.

Table I Distribution of age, sex, and presence of HBs antigen.

| Age (years) | Trial group Male | Female | Control group Male | Female |
|---|---|---|---|---|
| 30~39 | 2 | 1 | 5 | 2 |
| 40~49 | 13 | 4 | 12 | 5 |
| 50~59 | 41 | 24 | 42 | 19 |
| 60~69 | 17 | 14 | 19 | 18 |
| 70~ | 10 | 4 | 4 | 4 |
| Total | 83 | 47 | 82 | 48 |
| | 130 | | 130 | |
| Positive for HBsAg | 10 | 5 | 15 | 6 |
| | 15 | | 21 | |
| Negative for HBsAg heavy drinking | 23 | 0 | 31 | 2 |
| Negative for HBsAg blood transfusion | 8 | 15 | 11 | 12 |

Table II Liver dysfunction scores.

| Items \ Score | 0 | 1 | 2 |
|---|---|---|---|
| Serum bilirubin (mg/dl) | <1.4 | 1.5~2.9 | >3.0 |
| Serum albumin (g/dl) | >4.0 | 3.0~3.9 | <2.9 |
| Serum cholinesterase (ΔpH) | >0.60 | 0.40~0.59 | <0.39 |

Table III Patients with cirrhosis of the liver confirmed to have HCC.

| Patients | Trial group | Control group |
|---|---|---|
| Enrolled | 130 | 130 |
| Dropped out | 30 | 28 |
| Confirmed to have HCC | 12 | 21 |
| within the first 6 months | 3 | 4 |
| after the first 6 months | 9 | 17 |

## Results

Side effects were not reported in either group. HCC was found in 33 patients by the 34th month of the study. In the control group, four of the 21 patients found to have HCC were identified within the first 6 months and were thus excluded, three patients of 12 found to have HCC in the trial group were excluded for the same reason in the trial group (Table III).

The dropout rate included 28 patients in the control group, and 30 in the trial group. The incidence of HCC was lower in the trial group

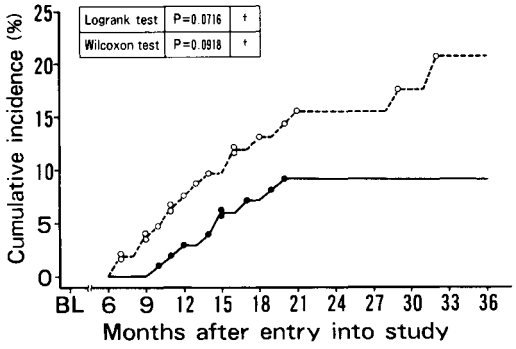


Fig. 1 Cumulative incidence of HCC detected 6 months or more after entry into the study.
Symbols : ● Sho-saiko-to group, ○ control group.

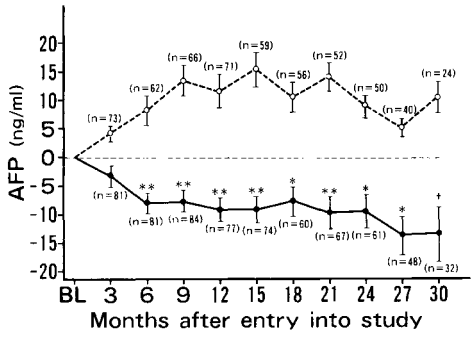


Fig. 2 Chage in AFP in patients not found to have HCC during the study.
Symbols : ● Sho-saiko-to group, ○ control group. $*p<0.05$, $**p<0.01$ : BL, base line.

($p = 0.0716$, log-rank test). Figure 1 shows the cumulative incidence of HCC in the two groups 6 months after the beginning of the study. The emergence of HCC was slower in the trial group than in the control group ($p<0.05$, Z-test). Table Ⅳ summarizes clinical features of the 26 patients who were found to have HCC. The size of the tumor detected was 3 cm in diameter or less in 24 of the patients and the remaining two patients had HCC of the diffuse type, which is difficult to detect by US.

Figure 2 shows changes in the AFP titer in the patients in both groups who were not found to have HCC during this study. The mean titer of AFP was significantly higher in the control group during the observation period.

Table Ⅳ Clinical features of the patients confirmed to have HCC.

| | Sex | Age | HBsAg | History of blood transfusion | History of heavy drinking | Time of detection from the beginning (months) | Diameter of tumor (mm) |
|---|---|---|---|---|---|---|---|
| Trial group | | | | | | | |
| 1 | M | 55 | − | + | + | 11 | 30×30 |
| 2 | M | 59 | − | − | − | 9 | 14×15 |
| 3 | F | 55 | − | − | − | 11 | 10×10 |
| 4 | M | 52 | − | − | − | 14 | 10×10 |
| 5 | M | 80 | − | − | − | 14 | 20×20 |
| 6 | M | 60 | − | − | + | 17 | 20×25 |
| 7 | F | 69 | − | + | − | 19 | 30×30 |
| 8 | M | 66 | + | − | − | 20 | 19×22 |
| 9 | M | 50 | − | − | − | 15 | 24×16 |
| Control group | | | | | | | |
| 1 | M | 54 | − | − | + | 8 | 18×14 |
| 2 | M | 59 | − | − | + | 11 | diffuse |
| 3 | M | 66 | − | − | − | 7 | 20×20 |
| 4 | M | 64 | + | + | + | 10 | 20×18 |
| 5 | M | 59 | − | + | − | 7 | diffuse |
| 6 | M | 57 | − | − | − | 9 | 15×11 |
| 7 | F | 48 | − | − | − | 11 | 20×30 |
| 8 | F | 55 | − | + | − | 12 | 10× 7 |
| 9 | M | 61 | − | − | + | 13 | 20×20 |
| 10 | M | 52 | − | − | − | 13 | 17×21 |
| 11 | F | 64 | − | + | − | 21 | 14×14 |
| 12 | M | 60 | − | + | − | 15 | 11×11 |
| 13 | M | 52 | − | − | − | 15 | 10×10 |
| 14 | F | 61 | − | + | − | 20 | 11×13 |
| 15 | M | 44 | − | + | − | 18 | 30×30 |
| 16 | M | 58 | − | − | + | 29 | 11×14 |
| 17 | M | 56 | − | + | + | 32 | 20×20 |

(1988.4)

## Discussion

The results show that Sho-saiko-to, one of the many formulations of traditional Oriental medicine, tends to delay the emergence of HCC. Cirrhotic patients are the most appropriate subjects for the evaluation of the preventive effects of drugs toward carcinoma in controlled prospective studies because although it is difficult to evaluate the preventive effect of medicines on carcinoma in humans, as evaluation requires a great number of subjects and an extended observation period, the yearly incidence of HCC in patients with cirrhosis is high (8%),[2] almost 80 times the rate of the detection of stomach cancer, the most common cancer in Japan, according to a gastroenterological survey.[7] Some risk factors (age, sex, presence of HBs antigen, *etc.*) for HCC are already known,[1,8] so patients with cir-

rhosis could be stratified according to risk factors. Also, as the technology of US apparatus has made remarkable progress in recent years, HCC in its very early stages can be detected efficiently and non-invasively by regular examination using US.

Many researchers have used immunomodulators as biological response modifiers in combination with anticancer agents against overt cancer, but this study used such an immunomodulator to inhibit the progression of latent cancer. Even a very small HCC comprises some hundreds of millions of cells. The first carcinoma cell is thought to appear several months or years before, and cell division was repeated often if the tumor was to become large enough to be detected clinically. It is reasonable that immunological treatment should be more efficient in the latent stage of HCC when the cancer cells are still few.

Sho-saiko-to is a combination of the crude extracts of seven herbs : Bupleuri Radix, Pinelliae Tuber, Sculellariae Radix, Zizyphi Fructus, Ginseng Radix, Glycyrrhizae Radix, and Zingiberis Rhizoma. Traditional Oriental medicine has developed over thousands of years on the basis of clinical experience and practice, and although some basic scientific knowledge of traditional Oriental medicine has been accumulated, chemical and pharmacological knowledge about these traditional medicines is still insufficient.

Bupleuri Radix, widely used in Asia for the treatment of hepatitis,[9] has as its active ingredient saikosaponin, the pharmacological mechanism of which has been investigated.[10] Haranaka *et al.*[4] administered traditional Oriental medicines to ddY mice in their drinking water before and after intradermal transplantation of Ehrlich tumors, and observed the development of the tumors and survival rate. The survival rate was high in the groups given Bupleuri Radix or Sho-saiko-to. Glycyrrhizine, the main component of Glycyrrhizae Radix, has also been reported to have antitumor effects. Takizawa *et al.*[11] reported that glycyrrhetic acid suppresses the promoting effect of 12-*O*-tetradecanoyl phorbol-13-acetate on skin tumors formed by treatment of mice with 7,12-demethyl benzanthracene. Their findings suggested that glycyrrhetic acid may interact with the plasma membrane to inhibit the binding of the tumor promotor to its receptor. Odashima *et al.*[12] reported an antitumor effect of ginsenosides, the main active ingredient of Ginseng Radix, which effect caused the reverse transformation of Morris hepatoma cells *in vitro*.

Although the possible interaction of the extracts of the herbs in Sho-saiko-to has not been studied, several reports about the antitumor effect of Sho-saiko-to have been made. Ogihara[5] administered Sho-saiko-to together with 3'-methyl-4-dimethylazobenzene in the drinking water of rats, and observed significant inhibition of the growth of induced HCC. Ito *et al.*[13] have reported that Sho-saiko-to when administered intraperitoneally and orally suppresses the growth of Ehrlich tumors in mice. Ito *et al.*[6] examined the antitumor effects of Sho-saiko-to with or without 5-fluorouracil or cyclophosphamide in an experimental system in mice of lung metastasis from Lewis lung carcinoma in mice. Sho-saiko-to which was administered orally, inhibited lung metastasis of carcinoma cells implanted into the footpads of the mice. Lung metastase were inhibited by the i.v. administration of peritoneal macrophages activated with Sho-saiko-to *per os*. Mizoguchi *et al.*[4] showed that Sho-saiko-to enhances the *in vitro* activity of natural killer cells, lymphokine-activated killer cells, and macrophages, and that it had antitumor effects.

This paper, to the best of our knowledge, is the first that reports a prophylactic effect of Sho-saiko-to against cancer in humans. In this still unfinished study, the incidence of HCC in the group given Sho-saiko-to was lower than in the control group. Sho-saiko-to may inhibit the growth of HCC by some immunological mechanism ; the data on AFP changes provide evidence for this assumption.

There are many questions still to be answered, such as by what mechanism does Sho-saiko-to inhibit the growth of carcinoma, what kinds of HCC can be prevented by Sho-saiko-to, and whether other medicines are superior to Sho-saiko-to in causing these effects. However, the

study groups such as those reported here should be useful for the evaluation of other medicines for the prevention of cancer in humans.

## 和文抄録

小柴胡湯は慢性肝疾患に有効とされ，実験的に抗腫瘍作用が認められている漢方薬であるが，我々は，小柴胡湯の肝癌に対する予防効果を評価するため，controlled prospective study を施行した。260名の肝硬変患者を年齢，性，HBs抗原，肝疾患の重症度の分布の等しい2群に分け，従来からの投薬を継続する対照群と，小柴胡湯7.5g/日投与群とに無作為に割り付けた。患者を34カ月間追跡し，両群の肝癌発生率を比較した。対照群で21例，投与群で12例の肝癌が発見された。研究開始時より相当の大きさで存在していた肝癌を除外するために6カ月目以降の発見例のみとすると，対照群17例，投与例9例となり，この結果から，小柴胡湯が肝硬変患者にける肝癌の発症を防いでいる，あるいは遅らせている可能性が示唆された。

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