Original

Inhibitory Effect of Kampo (Japanese Traditional Herbal Medicine) Therapy on the Development of Hepatocellular Carcinoma in Patients with HCV-related Chronic Hepatic Disease

—Usefulness of Kampo Therapy based on Traditional Theory—

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慢性 C 型肝炎患者の肝細胞癌発症に対する漢方治療の抑制効果

—伝統的な考え方に基づく漢方治療の有用性—

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Abstract

We evaluated the effect of Kampo therapy in which Kampo formulae were selected based on Japanese traditional theory, on the development of hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV)-related chronic liver disease. One hundred forty HCV-infected outpatients without HCC at their first examination and who were observed for more than one year, were included. The patients were divided into three groups according to the initial platelet count (Plt): Plt less than $10 \times 10^4/\mu\text{L}$ (Group I), Plt between $10 \times 10^4/\mu\text{L}$ and $14 \times 10^4/\mu\text{L}$ (Group II), and Plt greater than $14 \times 10^4/\mu\text{L}$ (Group III). For each patient, Kampo formulae were selected according to the patient's symptoms and physical findings at each clinic visit. The incidence of HCC calculated by the person-years method, was 0.89% in Group I, 1.55% in Group II and 0.29% in Group III. The annual incidence of HCC among our patients was low compared with that among untreated patients in previous reports. In addition, the incidence of HCC among our patients was low compared with that of previous studies where Shosaikoto or Juzentaihoto was administered for a long period of time. In the present study, age over 60 years was a possible risk factor for HCC. However, sex and patterns of the change in alanine aminotransferase level (ALT) were not associated with the development of HCC. A total of 53 different Kampo formulae were prescribed, for all patients, with Hochuekkito being the most frequent. These results suggest that Kampo treatment in which Kampo formulae are selected based on traditional theory, may be more useful than treatment by a single Kampo formula for preventing the development of HCC in patients with HCV-related chronic liver disease.

Key words: Kampo therapy, HCV-related chronic liver disease, Hepatocellular carcinoma, platelet count, Hochuekkito

要旨

伝統的な考え方に基づく漢方治療が肝細胞癌（HCC）発生抑制に有用であるか否かを検討した。対象は1年以上経過を観察し得た140例のC型慢性肝炎および肝硬変とし、初診時の血小板数により、3群に分類した。すなわち、血小板数が10万未満をⅠ群、10万以上14万未満をⅡ群、14万以上をⅢ群とした。漢方薬は受診ごとに自覚症状と身体所見を参考にして選択した。人年法によって求めたHCC年間発生率は、Ⅰ群で0.89% (95%CI: 0-2.63)、Ⅱ群で1.55% (95%CI: 0-3.31)、Ⅲ群で0.29% (95%CI: 0-0.88)であった。この結果は、従来報告されている未治療群におけるHCC発生率と比較して低値であり、また小柴胡湯あるいは十全大補湯単独で長期投与した報告と比較しても低値であった。初診時年齢60歳以上はHCC発症の危険因子と考えられたが、性別、ALT変動パターンとHCC発症には有意の相関が認められなかった。投与された処方53処方、最頻用処方は補中益気湯であった。以

上の結果から、伝統的考え方に基づく治療は、慢性C型肝炎患者におけるHCC発症抑制に有用であると考えられた。

キーワード：漢方治療、C型肝炎患者、肝細胞癌、血小板数、補中益気湯

Purpose

Hepatitis C virus (HCV)-related chronic liver disease (CLD) frequently develops into hepatocellular carcinoma (HCC). In Japan, approximately 7% of patients with liver cirrhosis (LC) develop HCC each year¹⁾²⁾. Continuous HCV infection causes chronic hepatitis (CH), and permanent eradication of HCV would achieve a complete cure. Interferon (INF) eradicated HCV in approximately 35-40% of patients with CH²⁾³⁾. Therefore, prevention of the development of CH to LC or inhibition of the development of HCC is difficult. On the other hand, a few studies have reported that Shosaikoto or Juzentaihoto, which are Kampo formulae, inhibited the development of HCC in patients with LC or CH^{4)~6)}. These reports suggested that Kampo therapy might be useful for preventing the development of HCC. In these studies, patients were administered a single Kampo formula. The clinical condition of patients with a chronic disease often changes over time. In Kampo therapy, the appropriate formula is selected based on the patient's clinical condition, and not on the patient's disease. If the Kampo formulae prescribed to a patient are changed according to the patient's signs and symptoms or according to the change in clinical

course, a stronger therapeutic effect would be expected. Therefore, the authors evaluated the effect of Kampo therapy in which Kampo formulae were selected based on Japanese traditional theory according to the patient's clinical symptoms at each clinic visit, on the development of HCC in patients with HCV-related CLD.

Subjects and methods

Subjects

We studied the effect of Kampo therapy based on Japanese traditional theory, on the development of HCC in 140 patients with HCV-related CLD who were seen for their initial consultation between March 1992 and March 2000 and who were followed for 1 year or longer (Table 1). HCC patients and patients who had HCC at the first consultation were excluded from the study. Based on recent reports that the platelet count (Plt) can be used to assess the degree of liver fibrosis¹⁾⁷⁾, the patients were divided into three groups according to the Plt at initial consultation: Plt less than $10 \times 10^4/\mu\text{l}$ (Group I); Plt greater than or equal to $10 \times 10^4/\mu\text{l}$ and less than $14 \times 10^4/\mu\text{l}$ (Group II); and Plt greater than or equal to $14 \times 10^4/\mu\text{l}$ (Group III). The median age at first consulta-

Table 1 Characteristics of patients with HCV-related CLD at first consultation and length of the observation period according to the platelet count

	Group I	Group II	Group III
Platelet count ($10^4 \times / \mu\text{l}$)	< 10	$10 \leq \sim < 14$	$14 \leq$
Patients, n	28	44	68
Sex, n (male/female)	8/20	16/28	28/40
Age (years) [median (range)]			
All*	60 (40-77)	60 (41-74)	58 (33-72)
Male	58 (40-72)	60 (42-74)	56 (36-70)
Female	60 (47-77)	62 (41-73)	59 (33-72)
ALT level (IU/L) (mean $\pm$ SD)			
All*	116 ± 68	103 ± 84	88 ± 77
Male	166 ± 101	90 ± 54	99 ± 54
Female	94 ± 41	110 ± 98	81 ± 78
Observation period (months) [median (range)]			
All*	44 (12-98)	52 (12-91)	62 (13-106)
Male	58 (12-82)	66 (14-91)	62 (15-105)
Female	32 (14-98)	50 (12-88)	62 (13-106)

ALT: alanine aminotransferase

* No significant differences in age and ALT level at first consultation and observation period among the three groups by Kruskal-Wallis test

Table 2 Kampo formulae with the ten longest administration periods among the patients with HCV-related CLD according to the class of Kampo medicine and the major signs and symptoms for their use

Class/	Kampo formula	% (n) *	Signs	Symptoms
Jingizai/				
	Hochuekkito	19.1 (95)	moist skin	severe malaise
	Juzentaihoto	3.4 (34)	dry skin	night sweating
Saikozai/			resistance and/or tenderness at hypochondrium	sleepy after meal
	Saikokeishito	13.5 (102)	contraction of rectus abdominis muscle	abdominal pain
	Saikokaryukotsuboreito	5.0 (23)	thick abdominal wall palpable pulsation of abdominal aorta	insomnia, anxiety palpitation
	Shosaikoto	3.4 (27)	moderately thick abdominal wall	sensitive to sound bitter taste
Ninjinzai/			resistance and/or tenderness at epigastrium	
	Rikkunshito	5.5 (60)	thin abdominal wall	anorexia
Kuoketsuzai/			paraumbilical resistance and/or tenderness	distended sense in lower abdomen
	Keishibukuryogan	8.8 (70)	telangiectasia of skin or mucous membrane dark red color of the lips, gums and oral mucous membrane	various menstrual disorders dryness of the mouth
Hojinzai/			feeling of emptiness and/or palpable linea alba beneath the umbilicus	nocturia, low back pain, burning sensation in palm and/or foot
Seinetsurisuzai/				
	Inchingoreisan	5.5 (34)	jaundice (not always apparent)	itching, thirst, small amounts of urine in spite of drinking water
	Inchinkoto	5.9 (34)		above symptom(s) + constipation

* * The administration period of a Kampo formula among the patients was expressed as the following percentage : [total number of months of administration of the indicated Kampo formula in the patients who received that Kampo formula] / [total number of months of observation of all patients] × 100%. "n" indicates the number of patients who received the indicated Kampo formula.

tion was 60 years in Group I, 60 years in Group II and 58 years in Group III, and there was no significant difference in the age at first consultation among the three groups. The mean ALT level at the first consultation was 116 IU/L in Group I, 103 IU/L in Group II, and 88 IU/L in Group III, showing no significant difference among the 3 groups. The median observation period was 44 months in Group I, 52 months in Group II, and 62 months in Group III, and there was no significant difference in the length of the observation period among the three groups. However, the median observation period among the women of Group I was 32 months and tended to be shorter than that among the women of Groups II and III. Sixty-four of the 140 subjects were lost to follow-up by the end of the study in March 2001 and no definite findings for HCC were observed in these cases. Sixteen of the 140 patients were treated with injection of glycyrrhizin during the study period, and 24 patients had previously been treated with INF therapy. The endpoint of observation of the patients was the date of development of HCC or March 31, 2001, whichever occurred earlier.

Methods

At each clinic visit, the particular Kampo formula was selected based on the patient's symptoms and physical findings. Among the 140 subjects in this study, 53 Kampo formulae were used. **Table 2** shows the ten Kampo formulae that were administered for the longest proportions of time of administration period to observation period (%), the number of patients who received each Kampo formula, and the major signs and symptoms for their use. Among these formulae, Keishibukuryogan, Hachimijiogan, Inchingoreisan and Inchinkoto were most frequently prescribed in combination with prescriptions of other drugs. Six formulae including Hochuekkito were mainly used for the treatment of CLD, and comprised 49.9% of all prescriptions. Each patient underwent a routine liver function test and measurement of tumor markers once a month and abdominal ultrasonography (US) every 3 months. If abdominal US detected space-occupying lesions (SOL), computed tomography, angiography and histological examination were performed to make a qualitative diagnosis. Patients with SOL who

Table 3 Pattern of the change in the annual mean ALT level and Incidence of HCC in Patients with HCV-related CLD

Group	Group I	Group II	Group III	All patients
Platelet count $\times 10^4/\mu\text{l}$	<10	$10 \leq < 14$	$14 \leq$	
Annual mean ALT level (n)				
High ($\geq 80\text{IU/L}$)	22	24	25	71
Low ($< 80\text{IU/L}$)	6	15	31	52
Fluctuating	0	5	12	17
Development of HCC (n)	1	3	1	5
Incidence of HCC [mean (95% CI)] ‡				
all	0.89 (0-2.63)	1.55 (0-3.31)	0.29 (0-0.88)	0.78 (0.10-1.46)
male	2.67 (0-7.91)	1.29 (0-3.18)	0	0.81 (0-1.94)
female	0	1.73 (0-4.13)	0.49 (0-1.46)	0.76 (0-1.61)
High ($\geq 80\text{IU/L}$)	1.19 (0-3.53)	1.77 (0-4.23)	0	0.95 (0-2.02)
Low ($< 80\text{IU/L}$)	0	1.92 (0-6.91)	0	0.42 (0-1.24)
Fluctuating	#	0	1.64 (0-4.86)	1.12 (0-3.32)

ALT : alanine aminotransferase

High : the annual mean ALT level persisted above 80 IU/L during observation period

Low : the annual mean ALT level persisted below 80 IU/L during observation period

Fluctuating : either the annual mean ALT level fluctuated above and below 80 IU/L or the annual ALT level was below 80 IU/L but an ALT elevation above 80 IU/L was observed two or more times a year

‡ calculated by using the person-years method [mean (95% CI)]

No patients in Group I belonged to the Fluctuating group

could not undergo these studies, were diagnosed as having HCC if they had growing SOL and/or increasing levels of tumor markers including AFP and PIVKA II levels.

The age at first consultation, sex, and the pattern of the change in the serum ALT level were investigated in relation to the occurrence of HCC to study the risk factors for HCC. The pattern of the change in the ALT level was classified as follows : Low, the annual mean ALT level during the observation period persisted below 80 IU/L ; High, the annual mean ALT level persisted at 80 IU/L or above ; and Fluctuating, either the annual mean ALT levels fluctuated above and below 80 IU/L, or the annual mean ALT level was below 80 IU/L but an ALT level above 80 IU/L was observed two or more times a year.

Statistical analyses

The incidence of HCC was estimated by the person-years method with 95% confidence interval (CI). Inter-groups difference was analyzed with the 95% CI of the difference in the means. The inter-groups difference in the age at first consultation, the ALT level at first consultation and length of the observation period was analyzed by Mann-Whitney's U-test or Kruskal-Wallis test using the Stat View program, version 4.5. $P < 0.05$ was considered to be significant.

Results

The pattern of the change in the ALT level, a higher percentage of patients in Group I had a persistently elevated ALT level than that in the other two groups (Table 3). During the observation period, one patient in Group

I, 3 patients in Group II and one patient in Group III developed HCC. Therefore, the incidence of HCC was 0.89% (95% CI : 0-2.63%) in Group I, 1.55% (95% CI : 0-3.31%) in Group II, and 0.29% (95% CI : 0-0.88%) in Group III. There was no significant association between Plt and the occurrence of HCC. Sex and pattern of the change in the ALT level were also not significantly associated with the occurrence of HCC. All patients who developed HCC were 60 years or older at the first consultation and the incidence of HCC among patients older than 60 years at the first consultation was 1.59% (95% CI : 0.20-2.98%). Among the 5 patients who developed HCC, one patient had previously received INF therapy ; one patient received injection of glycyrrhizin concomitantly with Kampo therapy ; and one patient received injection of glycyrrhizin concomitantly with Kampo therapy and had previously received INF therapy.

Discussion

In chronic hepatitis C, persistent infection of HCV causes hepatic fibrosis, leading to cirrhosis, and a high percentage of patients with cirrhosis develop HCC. There is no specific drug that can remove HCV or prevent the development of CH to LC. Patients who do not respond to INF have an intractable form. The extent of hepatic fibrosis is strongly related to the development of HCC, and liver biopsy is the most accurate tool for precise evaluation of liver fibrosis. Recently, it has been considered that the Plt is an alternative to liver biopsy for assessing

the degree of liver fibrosis¹¹⁷⁾. Obi reported that the Plt was correlated with the liver tissue findings in 80-90% of patients with HCV-related CLD: a Plt less than $10 \times 10^4/\mu\text{l}$ or less than $13 \times 10^4/\mu\text{l}$ corresponded to LC and severe CH, respectively, and the annual incidence of HCC was 7% and 3% among patients with Plt less than $10 \times 10^4/\mu\text{l}$ or less than $13 \times 10^4/\mu\text{l}$, respectively¹¹⁾. The author also reported that 21.6% of patients whose Plt decreased from $14 \times 10^4/\mu\text{l}$ or above to below $14 \times 10^4/\mu\text{l}$, and 16.4% of patients with a Plt remaining below $14 \times 10^4/\mu\text{l}$ during an average observation period of 3.2 years, developed HCC¹¹⁾. We classified our subjects with chronic hepatitis by Plt according to this previous study¹¹⁾, because we could not obtain histological findings by liver biopsy in the majority of our cases. In our study, none of the 14 patients whose Plt decreased from $14 \times 10^4/\mu\text{l}$ or above to less than $14 \times 10^4/\mu\text{l}$ during a median observation period of 5.3 years, developed HCC.

We compared the incidence of HCC among our patients (the person-years method) with that among patients with chronic hepatitis C in Japan according to the nationwide survey²⁾. In the nationwide survey, the incidence of HCC was 7.88% among patients in F 4 who were not treated with INF, 5.34% among patients in F 3, and 1.99% among patients in F 2. On the other hand, among patients treated with INF therapy, the incidence of HCC was 4.16% among those in F 4, 1.95% among those in F 3 and 0.58% among those in F 2. The majority of the patients in Group I were assumed to be in the F 4 stage, and the majority of the patients in Group II were assumed to be in the F 3 stage. Therefore, the incidence of HCC among our patients (0.89% in Group I, 1.55% in Group II and 0.29% in Group III) was lower than that among untreated patients and among INF-treated patients in the nationwide survey. These results suggest that Kampo therapy may be effective in inhibiting the development of HCC among patients with HCV-related CLD. However, it is difficult to compare the results of our study and those of the nationwide survey, because the follow-up study of cases who dropped out of our study was inadequate, and the evaluation method used to assign the stage of liver disease was different.

We also compared our results with the results of previous studies in which Kampo therapy was given to patients with HCV-related CLD. Oka et al⁵⁾ reported that the cumulative incidence of HCC (by the Gaynor's method) among patients with non-B LC who were treated with Shosaikoto during a 5-year period was 23%. In Higuchi's report⁶⁾, the cumulative incidence of HCC (by the Kaplan-Meier's method) among patients with type C LC who were treated with Juzentaihoto during an approximately 8-year period was approximately 40% (estimated from the graph in the report). The cumulative incidence of HCC among our cases was calculated by the Kaplan-Meier method, and the cumulative incidence of

HCC over an 8-year period was 8.3% in Group I. It is difficult to compare our results with the results of Oka et al⁵⁾ and Higuchi⁶⁾, because the types of hepatitis viruses, number of patients eligible for analysis, the eligibility criteria and analytical procedures were different. Nevertheless, the incidence of HCC among our patients who were treated with Kampo therapy in which the Kampo formula was selected according to the patient's symptoms based on Japanese traditional theory, was much lower than that among patients who were treated with a single Kampo formula^{5,6)}.

Risk factors for the development of HCC were investigated. Age, sex, and ALT level have been reported as risk factors for HCC. The median age at first consultation for HCV-related CLD among our cases was 60 years, and therefore our subjects were not considered to be younger than the subjects of previous studies (age over 50 or 60 years)^{81 ~ 101)}. All five patients who developed HCC were 60 years or older at the time of first consultation. The incidence of HCC among our patients with HCV-related CLD who were treated with Kampo therapy according to Japanese traditional theory, was low considering that our subjects did not include many younger patients.

Many reports suggested that male patients with type C CH were a high-risk group for the development of HCC^{3,81 ~ 101)}. Although we did not find a statistically significant difference in the incidence of HCC according to sex, the low proportion of male patients in our study compared with previous studies^{3,81 ~ 101)} may have influenced the low incidence of HCC in our study.

The incidence of HCC was reported to be higher among patients with a persistently high ALT level^{111 ~ 131)}. However, our results did not show a significant difference in the incidence of HCC among the High, Low, and Fluctuating groups. Tarao¹²⁾ reported that 24 (77.4%, annual incidence of 11.1%) of 31 patients with type C LC and a high ALT level (annual average level of 80 IU/L or more) developed HCC over a mean observation period of approximately 7 years, and 7 (20.6%, annual incidence of 2.6%) of 34 patients with a low ALT level (under 80 IU/L) developed HCC over a mean observation period of approximately 8 years. Among those who received concomitant administration of multiple prescriptions (mainly injection of glycyrrhizin with Shosaikoto or Juzentaihoto) in the present study the incidence of HCC at 5 years was 5.7% and its annual frequency was 1.1%. In the study of Tarao¹²⁾, the incidence of HCC among patients with a high ALT level and those with a fluctuating ALT level was 33.3% and the annual frequency was 6.7%. We calculated the incidence of HCC among our Group I patients using the method that had been used in their report. Among the Group I patients in the High ALT group, one patient developed HCC after 57 months and 6 patients were observed for more than 5 years; using their method, the incidence of HCC at 5 years was

14.3%, and its annual incidence was 2.86%. None of the three Group I patients with a low annual mean ALT level and who were followed for more than 5 years in our study, developed HCC.

We prescribed 53 Kampo formulae among the patients in this study. Each patient received 1 to 22 formulae, with a median of 7 formulae. The ten Kampo formulae that were administered to our patients for long periods of time, according to the class of Kampo medicine, were ninjinogizai (Hochuekkito, Juzentaihoto), saikozai (Saikokeishito, Saikokaryukotsuboreito, Shosaikoto), ninjinzai (Rikkunshito), hojinzai (Hachimijogan), kuoketsuzai (Keishibukuryogan), and seinetsurisuzai (Inchinkoto and Inchingoreisan). Among these formulae, experimental studies showed that Hochuekkito¹³⁾, Saikokeishito¹⁵⁾, Juzentaihoto¹⁴⁾¹⁶⁾, Shosaikoto¹⁷⁾¹⁸⁾ and Rikkunshito¹⁹⁾ have an antitumor or immunostimulant effect, and these pharmacological effects might have contributed to lowering the incidence of HCC.

We diagnosed the “sho” (evidence) (syndromes including patient’s constitution) in the patients with CLD according to the procedures of Kampo medicine, and selected appropriate Kampo formulae at each visit. Our results suggest that the “sho” of a patient with CLD is more similar to kyosho (the condition of decreased physical strength or energy) than to the “sho” of Shosaikoto which has been used in most patients with HCV-related CLD. Furthermore, the Kampo medicines of kuoketsuzai (a drug that improves microcirculation), seinetsurisuzai (a drug that improves inflammation and water metabolism) and hojinzai (a drug that enhances immunity and vitality) were often used in combination with another drug(s). From the viewpoint of Kampo medicine, it is difficult to consider that the clinical condition of patients with chronic hepatitis would be constant for several years and that they could be treated with the same formula of Kampo medicine. Therefore, close management is required for the treatment of CLD. Our study suggests that Kampo therapy in which Kampo formulae were selected based on the patient’s clinical symptoms according to Japanese traditional theory, that is, appropriate changes in prescription were made according to the patient’s clinical signs and symptoms, may prevent the development of HCC in patients with HCV-related CLD. The combination of Western medicine with such Kampo approach will improve the treatment of chronic hepatic diseases.

Conclusions

We evaluated whether Kampo therapy in which particular Kampo formulae are selected based on the patient’s clinical symptoms according to Japanese traditional theory, can prevent the development of HCC in patients with HCV-related CLD. The incidence of HCC among patients with type C CH was investigated, and our

conclusions are as follows :

- 1) Patients with HCV-related CLD were classified according to Plt into 3 groups, that is, Plt below $10 \times 10^9/\mu\text{l}$, Plt between $10 \times 10^9/\mu\text{l}$ and $14 \times 10^9/\mu\text{l}$, and Plt above $14 \times 10^9/\mu\text{l}$, and the incidence of HCC (the person-years method) in each group was investigated. The incidence of HCC was 0.89%, 1.55%, and 0.29%, respectively, and these values are lower than those in previous reports.
- 2) Sex and the pattern of the change in the ALT level were not associated with the development of HCC. However, the age at first consultation for HCV-related CLD of over 60 years was thought to be a possible risk factor for HCC.
- 3) A total of 53 Kampo formulae were prescribed to our patients, and Hochuekkito was the Kampo formula that was administered for the longest period of time among our patients.
- 4) Kampo therapy based on Japanese traditional theory is considered to be useful in suppressing the development of HCC in patients with HCV-related CLD.

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