The effectiveness of traditional Japanese medicine (Kampo), in combination with pegylated interferon α plus ribavirin for patients with chronic hepatitis C: A pilot study

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Abstract

Background: Kampo medicine has been shown to be useful for reducing the adverse effects of pegylated interferon (PEG-IFN) α-2b plus ribavirin (RBV). The study was done to determine if Kampo would have a synergistic effect with PEG-IFNα-2b plus RBV that would improve their effectiveness in the treatment of chronic hepatitis C.

Methods: From a total of 51 chronic hepatitis C virus (HCV) patients, 26 received PEG-IFNα-2b plus RBV treatment combined with Kampo medicine (group A) and 25 received only the standard treatment (group B). Group B patients were prescribed a mixture of shimbuto and ninjinto extract to be taken three times a day before meals.

Results: The early virological response (EVR) and sustained virological response (SVR) rates were significantly higher in group A than in group B (EVR: 84.6%, 22 of 26 vs 56.0%, 14 of 25, P=0.034: SVR: 76.9%, 20 of 26 vs 48.0%, 12 of 25, P=0.033). 22 of 26 patients in group A (84.6%) and 18 of 25 patients in group B (72.0%) received at least the minimum acceptable dosage (at least 80% or more of the target PEG-IFNα-2b and 60% or more of RBV) during treatment, with no significant between group difference in the rate of SVR.

The discontinuation rate was significantly lower in group A, in which no patients discontinued, than in group B (20.0%, 5 of 25) (P=0.023).

Conclusions: A mixture of shimbuto and ninjinto reduced the discontinuation rate and improved the treatment efficacy of patients with chronic HCV treated with PEG-IFNα-2b plus RBV.

Key words Kampo medicine, Hepatitis C virus, pegylated interferon, ribavirin.

Abbreviations AFP, alpha-fetoprotein; ANOVA, Analysis of variance; EVR, Early virological response; Hb, hemoglobin level; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; PEG, pegylated; Plt, platelet count; RBV, ribavirin; SD, standard deviation; SVR, Sustained virological response; Th, T-helper cell; WBC, white blood cell count.

Introduction

It is well known that hepatocellular carcinoma (HCC) caused by HCV infection usually develops in patients with advanced chronic Hepatitis and liver cirrhosis. Interferon (IFN) therapy for chronic hepatitis C is useful for eliminating HCV and for reducing the progression of hepatic fibrosis and the consequent development of HCC. Antiviral treatment for chronic hepatitis C has been greatly improved, with the currently accepted initial treatment a combination of
pegylated (PEG)-IFNα plus ribavirin (RBV). However, adverse effects by patients receiving the combination treatment are more common than by patients receiving IFN monotherapy.6,7) The most frequent adverse effects during PEG-IFNα and RBV treatment are general fatigue, depression and hematological disorders such as leukopenia and anemia. Furthermore, the rate of discontinuation due to adverse effects was reported to be significantly higher for patients aged 65 years or over than for those under 65 years.8-11) We previously reported that a minimum acceptable dose of at least 80% of the target dosage of PEG-IFNα-2b and 60% of the target dosage of RBV is necessary for the successful treatment of Japanese patients with genotype 1, even for elderly patients.8,9,12) To maximize adherence to the optimal treatment regimen, it is necessary to control for adverse effects that might interrupt treatment. Most elderly patients with chronic hepatitis have severe liver problems, such as cirrhosis. Because they are vulnerable to the development of HCC, it is important that they receive timely IFN therapy.

We previously reported that one of Kampyo medicines, maoto (Mahaung-tang) is useful for reducing adverse effects, such as flu-like symptoms and psychological symptoms.13-15) In a similar way, our experience has shown that Kampyo medicine is effective for reducing the adverse effects of PEG-IFNα-2b and RBV. Based on these observations, this pilot study was done to give empirical evidence of the effectiveness of the commonly prescribed combination regimen when Kampyo medicine is added.

Methods

Patients: A total of 51 patients (20 men and 31 women, 56.5±11.5 years) with chronic hepatitis C were enrolled for study between October 2008 and March 2010. All were positive for antibody to HCV and HCV RNA for over six months.

Patients who fulfilled the following criteria were recruited from the Department of General Internal Medicine of Kyushu University Hospital, Iizuka Hospital, Okabe Hospital, Kyushu-chuo Hospital, Hara-Doi Hospital and Mitsutake Hospital.

Exclusion was for the following reasons: (i) clinical or biochemical evidence of hepatic decompensation, advanced cirrhosis identified by bleeding-risky esophageal varices, history of gastrointestinal bleeding, ascites, encephalopathy, or HCC; (ii) hemoglobin level (Hb)<115g/L, white blood cell count (WBC)<3×10^9/L, and platelet count (Plt)<50×10^9/L; (iii) concomitant liver disease (hepatitis B surface antigen positive or human immunodeficiency virus positive); (iv) excessive active alcohol consumption>60g/day or drug abuse; (v) severe psychiatric disease; or (vi) antiviral or corticosteroid treatment within 12 months prior to enrollment.

Each patient was tested for alpha-fetoprotein (AFP) and had abdominal ultrasonographic examination within the three months before the start of treatment and every three months during the treatment period. If an abnormal AFP level of 40ng/mL and/or focal lesions on ultrasonographic examination were found at any testing, further testing for HCC was done, which included dynamic computed tomography, angiography, and/or tumor biopsy. Patients so confirmed to have HCC within three months after the start of treatment were excluded.

Table 1 shows the baseline clinical characteristics of the enrolled patients, 26 of whom were randomly assigned to a Kampyo treatment group (group A) and the remaining 25 to a control group (group B). The groups were similar in baseline characteristics.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of each participating hospital. Informed consent was obtained from all patients before enrollment. The study was registered as a clinical trial on the University Hospital Medical Information Network (ID 000007068).

Treatment regimen: All patients were genotype 1b, and were treated with a weight-based, 1.5 μg/kg weekly dose of subcutaneous PEG-IFNα-2b (PegIntron, MSD, Tokyo, Japan), in combination with RBV (Rebetol, MSD, Tokyo, Japan), which was given orally at a daily dose of 600-1000 mg based on body weight (600 mg for patients weighing less than 60 kg, 800 mg for those weighing 60-80 kg, and 1000 mg for those weighing 80 kg or over). The length of treatment was 48 weeks, and the above duration and dosage are those approved by the Japanese Ministry of Health, Labor and Welfare.
Table 1 Characteristics of 51 chronic HCV infected patients treated with a combination of pegylated IFNα plus RBV

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=26)</th>
<th>Group B (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>9 (34.6)</td>
<td>11 (44.0)</td>
<td>0.493</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.1±11.2</td>
<td>55.8±12.0</td>
<td>0.208</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>23.4±3.5</td>
<td>22.0±2.5</td>
<td>0.208</td>
</tr>
<tr>
<td>Prior non-pegylated IFN monotherapy n (%)</td>
<td>9 (34.6)</td>
<td>11 (44.0)</td>
<td>0.492</td>
</tr>
<tr>
<td>Prior combined non-pegylated IFN plus RBV treatment n (%)</td>
<td>6 (23.1)</td>
<td>5 (20.0)</td>
<td>0.789</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>76.8±26.4</td>
<td>67.5±44.8</td>
<td>0.228</td>
</tr>
<tr>
<td>γ-Glutamyltranspeptidase (IU/L)</td>
<td>68.5±82.3</td>
<td>52.2±49.3</td>
<td>0.977</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>40.9±3.5</td>
<td>38.9±3.6</td>
<td>0.057</td>
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<tr>
<td>White blood cell (×10⁹/L)</td>
<td>5.1±1.2</td>
<td>4.6±1.6</td>
<td>0.178</td>
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<tr>
<td>Hemoglobin (g/L)</td>
<td>138.3±16.0</td>
<td>135.9±15.5</td>
<td>0.821</td>
</tr>
<tr>
<td>Platelet count (×10⁹/L)</td>
<td>168.8±44.8</td>
<td>169.8±45.5</td>
<td>0.547</td>
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<tr>
<td>Creatinine (µmol/l)</td>
<td>57.1±15.8</td>
<td>55.8±13.6</td>
<td>0.655</td>
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<tr>
<td>Total cholesterol (mmol/l)</td>
<td>3.9±1.7</td>
<td>4.4±1.0</td>
<td>0.942</td>
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<tr>
<td>Tryglyceride (mmol/l)</td>
<td>0.9±0.5</td>
<td>0.9±0.4</td>
<td>0.375</td>
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<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>101.0±9.8</td>
<td>89.3±12.9</td>
<td>0.618</td>
</tr>
<tr>
<td>Serum HCV RNA level (logIU/mL)</td>
<td>6.0±0.6</td>
<td>6.3±0.7</td>
<td>0.429</td>
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<tr>
<td>APRI</td>
<td>1.4±0.9</td>
<td>1.4±1.1</td>
<td>0.572</td>
</tr>
<tr>
<td>Histological fibrosis</td>
<td>0.955</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F0/F1/F2/F3/F4 not data 1/10/5/2/1 7 6/6/7/5/1 0

Data are shown as the mean±standard deviation
Group A: combination of pegylated IFNα plus RBV with a Kampo treatment, Group B: combination of pegylated IFNα plus RBV
APRI: aminotransferase to platelet ratio index  AST(IU/L)/upper limit of normal (IU/L)×100/platelets (10⁹/L)

Patients were considered to have RBV-induced anemia if the hemoglobin level decreased to less than 100 g/L. In such cases, a reduction in the dosage of RBV was required. Some patients also had PEG-IFNα-2b-induced psychological adverse effects or a decrease of white blood cell or platelet count. In such cases, a reduction in the dose of PEG-IFNα-2b was required. Both PEG-IFNα-2b and RBV were discontinued if the hemoglobin level, white blood cell count, or platelet count fell below 85 g/L, 1×10⁹/L, or 25×10⁹/L, respectively. The treatment was discontinued if severe general fatigue, hyperthyroidism, interstitial pneumonia, or severe hemolytic problems developed, continuation of treatment was judged not to be possible by the attending physician, or the patient desired discontinuation of treatment.

Kampo medicine: Patients were prescribed Kampo medicine, a mixture of shimbuto (Zhenwu-tang) and ninjinto (Renshen-tang) extract to be take three times a day (each dose 5g) before meals. 15g of shimbuto and ninjinto extract granules contains 4.0g of a dried extract of the following nine mixed crude drugs: JP Poria Sclerotium 4.0g, JP Ginseng 3.0g, JP Glycyrhriza 3.0g, JP Processed Ginger 3.0g, JP Powdered Processed Aconite Root 0.5g, JP Ginger 1.5g, JP Zingiberis Rhizoma 4.5g, JP Peony Root 3.0g, JP Atractylodis Lanceae Rhizoma 6.0g.

Determination of baseline HCV RNA level and HCV genotype: The pretreatment, baseline, serum HCV RNA level was measured by COBAS TaqMan HCV test (TaqMan) (Roche Diagnostics, Tokyo, Japan). TaqMan assay has a lower limit of quantitiation of 15 IU/mL and an outer limit of quantitiation of 6.9×10⁷ IU/mL (1.2 to 7.8 logI/U/mL referred to log10 units/mL). Therefore, TaqMan assay is able to do both qualitative and quantitative analysis for HCV RNA. The HCV genotype was determined by type-specific primers of the 5'-non-coding region of the HCV genome. The protocol for genotyping was carried out as previously described.2)
Efficacy of treatment: Early virological response (EVR) and Sustained virological response (SVR) were defined as serum HCV RNA undetectable at within 12 weeks from start and the 24 weeks follow-up after the end of treatment, respectively. EVR and SVR were defined as non-detectable HCV-RNA, as measured by TaqMan test, with the results labeled as positive or negative. The analysis of the EVR and SVR rates were done on an intention-to-treat basis.

Liver histology: Liver biopsy was done for 19 (73.1%) of the group A and 25 (100%) of the group B patients. The other patients refused biopsy. Fibrosis was staged on a 0-4 scale as follows: F0=no fibrosis, F1=portal fibrosis without septa, F2=portal fibrosis and few septa, F3=numerous septa without cirrhosis, F4=cirrhosis. Liver fibrosis was not significantly advanced in either the group A or B patients (P=0.955).

Minimum acceptable dosage: We previously reported that the minimum acceptable dosage necessary for Japanese genotype 1 patients to obtain an SVR is at least 80% of the target dosage of PEG-IFNα-2b and that the minimum acceptable dosage of the target RBV is 60%. Therefore, we compared the SVR rates of patients in the with Kampo treatment group and a control group who received at least 80% or more of the target dosage of PEG-IFNα-2b and 60% or more of the target RBV (minimum acceptable dosage).

Statistical analysis: Continuous data are expressed as mean values, the values ± standard deviation (SD) of the mean. The statistics were done using a commercially available software package (BMDP Statistical Software Inc., Los Angeles, CA, USA) for the IBM 3090 system computer. The chi-squared test, Student’s t-test and Fisher’s exact test were used to determine differences in the baseline clinical characteristics, safety, efficacy of the combination therapy, adherence to the total dose, and the association between adherence, EVR and SVR. Repeated measure ANOVA (Analysis of variance) was used for comparison of the changes of blood cell counts. A P-value of less than 0.05 was considered significant.

Results

EVR and SVR by intention-to-treat analysis: The EVR rate was significantly higher in group A (22 of 26, 84.6%) than in group B (14 of 25, 56.0%) (P=0.034), and the overall SVR rate was significantly higher in group A (20 of 26, 76.9%) than in group B (12 of 25, 48.0%) (P=0.033) (Fig.1). In comparison by sex, no significant difference was found in the SVR rate (men: Kampo, 7 of 9, 77.8% vs ctrl, 4 of 11, 36.4%, P=0.092, women: Kampo, 13 of 17, 76.5% vs control, 8 of 14, 57.1%, P=0.441). Furthermore, no significant difference in the SVR rate was found by age (under 65 years old: Kampo, 13 of 18, 72.2% vs control, 8 of 19, 42.1%, P=0.065, 65 years and over: Kampo, 7 of 8, 87.5% vs control, 4 of 6, 66.7%, P=0.539).

![Graph showing EVR and SVR rates for Group A and Group B](image)

**Fig. 1** Early virological response and Sustained virological response by intention-to-treat analysis

Analysis of the SVR rates of patients who adhered to the treatment regimen and completed treatment with at least the minimum acceptable dosages of PEG-IFNα-2b plus RBV: Within 12 weeks, 92.3% (24 of 26) in group A who received at least the minimum acceptable dosage had achieved a SVR, as had 92.0% (23 of 25) in group B. Within 48 weeks the rates were 84.6% (22 of 26) for group A and 72.0% (18 of 25) for group B, with no significant difference. When the patients received at least the minimum acceptable dosage during treatment, the SVR rate was not
significantly different between groups A and B (17 of 22, 77.3% and 12 of 18, 66.7%, respectively). However, when the patients did not receive at least the minimum acceptable dosage, the SVR rate was significantly higher in group A (3 of 4, 75.0%) than in group B (0 of 7, 0%) (P=0.024). Furthermore, analysis of the association of sex and age with the SVR rate of patients who received at least the minimum acceptable dosage during treatment, found no significant difference between groups A and B (men: 6 of 8, 75.0% vs 4 of 7, 57.1%, P=0.608; women: 11 of 14, 78.6% vs 8 of 11, 72.7%, P=1.000; under 65 years: 11 of 14, 78.6% vs 8 of 14, 57.1%, P=0.420; over 65 years: 5 of 6, 83.3% vs 4 of 4, 100%, P=1.000).

**Discontinuation of PEG-IFNα-2b plus RBV treatment and adverse effects:** The discontinuation rate was significantly lower in group A, in which no patients discontinued, than in group B (20.0%, 5 of 25) (P=0.023). Group B patients discontinued the treatment because of adverse effects; vertigo (1 at 4 weeks), interstitial pneumonia (1 at 10 weeks), hyperthyroidism (1 at 22 weeks), and the occurrence of HCC (1 at 19 weeks); and one patient discontinued treatment because there was no efficacy at 44 weeks. No significant differences in the WBC, Hb, or Plt were found between groups A and B during the treatment period (Fig. 2).

**Discussion**

This is the first report of a Kampo medicine having a synergistic effect with the currently recommended interferon treatment that leads to an increased SVR rate for chronic hepatitis C patients. Only one paper has been published on this topic. Unfortunately, it is written in Chinese and the description of the herbs used is unclear, which limits the access to and ability to repeat

![Fig. 2](http://example.com/fig2.png)

**Fig. 2** Blood cell concentration during treatment
No significant differences in the White blood cell (A), Hemoglobin (B), or Platelet counts (C) were found between groups A (■) and B (●) during the treatment period.
the study.

PEG-IFNα-2b, a protein-conjugate containing a single straight-chain peg with a molecular weight of 12,000 daltons and interferon alpha-2b in a 1:1 ratio, maintains its antiviral activity but has an approximately 10-fold longer plasma half-life than IFNα-2b in human studies. Because PEG-IFNα remains for a long time at therapeutic blood levels, the patient's metabolism slows, their extremities become cold, and they feel general fatigue.

Shimbuto is usually prescribed for general malaise and vertigo with cold in the interior layers of the body, and ninjinto is usually prescribed for mental and physical exhaustion. Therefore, we felt that a mixture of shimbuto and ninjinto would be useful in combination with PEG-IFNα plus RBV. In clinical practice, our experience shows that this mixture of shimbuto and ninjinto is effective in reducing the adverse effects associated with PEG-IFNα plus RBV, such as general malaise and depression. Thus, we used this mixture of shimbuto and ninjinto for the patients of this study.

The reason why adding the mixture of shimbuto and ninjinto resulted in an increased SVR rate is that the discontinuation rate was significantly lower with the Kampo medicine than in the standard combination treatment group. Previous studies have reported discontinuation rates due to adverse effects was of 10 - 14% with HCV genotype 1b, with the most common reason for discontinuation being general malaise and depression. Further, previous studies reported that the rate of discontinuation due to adverse effects was significantly higher by patients aged 65 years or over than by those under 65 years. This high incidence of discontinuation due to adverse effects was considered to be one of the reasons why older patients did not respond well to IFNα. In this small study, none of the patients discontinued the treatment because of general malaise, thus we could not show conclusively that this mixture of shimbuto and ninjinto is effective for reducing this side effect. However, our previous data demonstrated that the discontinuation rate due to adverse effects when the mixture of shimbuto and ninjinto is added is very low compared with previous studies, regardless of age, suggesting that this Kampo medicine is effective, especially for older patients.

The antiviral effects of the mixture of shimbuto and ninjinto for HCV are unclear. It has been reported that both viral and host factors, such as T-helper cell (Th1/Th2 ratio, are important to the elimination of HCV. The mixture of shimbuto and ninjinto warms the body and increases the metabolism, which might increase the immunological response. Kampo medicine acts as an immunomodulator and in our experience, has the advantage of warming and improving metabolism that other medicines lack.

Other Kampo medicines have been used to reduce adverse effects associated with chemotherapy for cancer, and we feel that combination therapies including both of Kampo medicine and western medicines will be used to treat many other diseases in the future.

In conclusion, we demonstrated that a mixture of shimbuto and ninjinto reduced the discontinuation rate and improved the treatment efficacy of patients with chronic HCV treated with PEG-IFNα-2b plus RBV, regardless of age. Because this was a pilot study, further studies of larger scale will be necessary.

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Disclosure Statement

No competing financial interests exist.

References


