

Three step primary liver cancer prevention program utilizing dynamic tumor marker combination assay in high-risk patients with chronic hepatitis

Abstract

Background: For the past 30 years, our efforts have focused on the primary prevention of cancer through the use of a tumor marker combination assay.¹ However, an understanding has been difficult to achieve owing to the expansion of organ-specific medicine. Patients with hepatitis B (HBV) and C virus (HCV) infections have about a 10-fold higher risk of liver cancer than individuals without viral hepatitis. We therefore focused on high-risk patients with viral hepatitis to study the effectiveness of a three-step liver cancer prevention program over the course of 10 years.

Methods: The risk of cancer was assessed on the basis of the results of a dynamic tumor marker combination assay and conventional liver-function tests. The 406 subjects included 54 patients with chronic HBV hepatitis infection and 352 patients with chronic HCV hepatitis infection. Interventional studies of methods to predict and prevent the development of liver cancer were performed. The high risk subjects were treated with holistic methods that included dietary and life style change (dietary energy restriction) as well as a high dose of vitamin C, vitamin A, branched-chain amino acid granules and vitamin K2 as the first step. Intake of herbal medicine (Sun Advance) and detoxifying therapy constituted the second step, and local radio-frequency hyperthermia was the third step of liver cancer prevention program.

Results: In the 406 patients with chronic hepatitis, the response to treatment to prevent the development of liver cancer in this 10-year survey was as follows: improvement was obtained in all 136 patients with mild hepatic fibrosis (F1) and 144 patients with moderate hepatic fibrosis F2. Among the 49 patients with advanced fibrosis F3, 34 improved, but 15 did not show no improvement. Among the 77 patients with cirrhosis (F4), 44 patients improved, while 33 patients showed no signs of improvement. Our three-step primary liver cancer prevention program thus effectively prevented the development of liver cancer in 99% of high-risk patients with chronic hepatitis. Liver cancer developed in only 3 patients (0.7%).

Conclusion: Our three-step liver cancer prevention program effectively prevented the development of liver cancer in high-risk patients with chronic hepatitis.

Keywords: liver cancer prevention program, high dose vitamin C, vitamin A intake, branched-chain amino acid granules, vitamin K, herbal medicine (sun advance), detoxifying treatment

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Introduction

The increased prevalence of hepatitis C virus (HCV) infection has led to higher mortality rates from liver cancer in Japan. We have conducted a three-step primary cancer prevention program utilizing a dynamic tumor marker combination assay to comprehensively prevent all types of cancer in 21000 subjects over the course of 30 years.¹ However, it has been difficult for Western physicians to understand systemic cancer prevention programs because Western medicine focuses on specific organ systems. On the other hand, hepatologists have reported that branched-amino acid granules inhibit liver carcinogenesis in patients with severe liver cirrhosis.² We therefore focused on the prevention of liver cancer among patients with chronic hepatitis and patients with liver cirrhosis over a period of 10 years applying a three-step primary liver cancer prevention program utilizing a tumor marker combination assay and routine laboratory examination. Recently, Narumiya et al have shown that vitamin A-storing hepatic stellate cells clearly participate in hepatocytes

fibrosis in a mouse model of immune-mediated hepatitis.³ We have long studied the relations of vitamin A concentrations to immunity and liver fibrosis. The degree of fibrosis was classified from F₀ to F₄ according to the criteria proposed by Japan Society of Hepatology.

The vitamin A serum concentration, white blood cell (WBC) count, T cell count, and natural killer (NK) cell activity at initial presentation were measured in 44 patients with chronic hepatitis, among whom 40% had HBV hepatitis and 60% had HCV hepatitis (Table 1). Patients with mild hepatitis with no progression of fibrosis were classified as F₀. As hepatitis-related fibrotic changes progressed from F₁ to F₄, the vitamin A serum concentration, WBC count, T-cell count, and natural killer (NK) cell activity progressively decreased (Table 1). On the basis of these data, we established a global strategy for treatment. Patients with liver cancer, immuno suppression, or chronic inflammation were given high-dose vitamin C therapy. Patients with fibrosis received vitamin A supplementation, and patients with evidence of liver cancer cells received herbal medicine (Sun Advance),

branched-chain amino acid granules, and vitamin K₂ (Glakay). Patients with immuno suppression were given detoxification therapy as part of this comprehensive treatment strategy. If evidence of liver cancer was detected, local radio-frequency was performed. Vitamin A

was measured using the methods of Thompson et al.⁴ Immune activity was measured using the method of Hoffman RA et al.⁵

Examination data were obtained from 44 viral chronic hepatitis patients.

Table I Degree of hepatic fibrosis risk classification

	F ₀	F ₁	F ₂	F ₃	F ₄
Vitamin A	65.5(±16.5)□	44.8±40.5□	32(±51)	28.7(±3.6)	16.8(±34)
WBC	5950±1970	4740(±900)	3807(±2900)	3994(±1300)	
T cell □	1837(±60)	1449(±184)	908(±130)	700(±260)	
Stimulation Index (SI)	230(±39)	137(±85)	190(±59)	184(±116)	
NK cell	34(±15)	33(±14)	27(±8)	26(±10)	

Vitamin A was determined by Thompson et al.⁴ method.⁴

Immune activity was measured by the method of Hoffman RA et al.⁵

Examination data are obtained from 44 viral chronic hepatitis patients.

Subjects and materials

The study group comprised a total of 406 patients, including 54 patients with chronic HBV hepatitis infection and 352 patients with chronic HCV hepatitis infection. Seventy-seven patients had liver cirrhosis (F₄). Their ages ranged from 24 to 72 years. The degree of fibrosis was classified from F₀ to F₄ according to the criteria proposed by the Japan Society of Hepatology, which are based on the platelet count, hyaluronic acid concentration, type IV collagen concentration, and cholinesterase activity. In the patients with HBV hepatitis, fibrosis was F₁ in 10 patients, F₂ in 16 patients, F₃ in 19 patients, and F₄ in 9 patients. In the patients with HCV hepatitis, fibrosis was F₁ in 126 patients, F₂ in 128 patients, F₃ in 30 patients, and F₄ in 68 patients. Evaluation criteria were based on the improvement of the following liver function data (GOT, GPT, choline esterase, total bile acid, adenosine deaminases (ADA), platelet number, albumin, γ -globulin and γ - glutamyl transpeptidase (γ -GTP) The criteria of conventional liver function tests are as follows.: platelet F₁ ($18 \times 10^4 / 1 \text{mm}^3 >$), F₂ ($15 \times 10^4 / 1 \text{mm}^3 >$), F₃ ($13 \times 10^4 / 1 \text{mm}^3 >$) and F₄ ($10 \times 10^4 / 1 \text{mm}^3 >$) and hyaluronic acid (F₁, F₂: under 50ng/ml, F₃:50-80ng/ml and F₄: over 80ng/ml) and 4 type of collagen(F₁, F₂: under 150ng/ml, F₃: 150-200ng/ml and F₄: over 200ng/ml) and choline esterase value (F₁, F₂: under 230U/L, F₃:230-150/L and F₄: under 150U/L). In the patients with HBV hepatitis, fibrosis was F₁ in 10 patients, F₂ in 16 patients, F₃ in 19 patients, and F₄ in 9 patients. In the patients with HCV hepatitis, fibrosis was F₁ in 126 patients, F₂ in 128 patients, F₃ in 30 patients, and F₄ in 68 patients.

Our liver primary cancer prevention program consisted of three steps.

- 1. First step:** The patients were recommended to stop smoking, stop drinking alcoholic beverages, avoid over work, increase their intake of green and yellow vegetables, take a high dose (>6g) of vitamin C daily,^{6,7} and to take three 20mg tablets of retinol palmitate (Chocola A) daily until their serum vitamin A level reached 700 $\mu\text{g}/\text{dL}$.⁸⁻¹⁰ Branched-chain amino acid granules (12g/day)² and vitamin K₂ (Glakay 45mg/day)¹¹ were also recommended.
- 2. Second step:** If the first step was not effective, the patients were given intravenous infusions of high dose of vitamin C (20-30g) one or two times per week.^{6,7} Detoxification therapy was given

one to three times per week. As shown in Figure 1, the one to two high doses of vitamin C per week were effective in nearly all patients. Patients who did not respond to these treatments were given herbal medicine (Sun Advance, 1.6 gram per day, Chiba City IMHC Clinic, which inhibits aerobic respiration of cancer cells.¹²⁻¹⁴ Detoxification therapy was performed by the Nishi health therapy technique, using a Nishi-type device (Orthopedic Traction Apparatus, WA 57B (686) Yamato KK, Ehime Prefecture, Japan). Exercise therapy was performed for 20 to 30minutes). To cleanse the colon, the patients orally ingested a detoxification preparation consisting of citric acid (12g) lactulose (24g, Kowa, Tokyo, Japan), and magnesium hydroxide(30g) dissolved in 50ml of water.

- 3. Third step:** If no improvement was observed, radio-frequency treatment (local hyperthermia)¹⁵⁻¹⁸ was recommended.

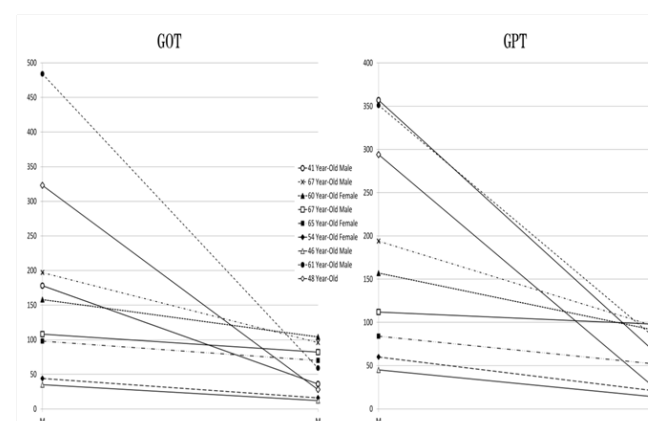


Figure 1 Shows the effects of high-dose vitamin C on aspartate transaminase (GOT). And alanine transaminase (GPT) in chronic viral hepatitis patients GOT and GTP values before and after high-doses of vitamin C (20-30grams) treatment 1 or 2times per week (total of 10times), or every day for 10days in severe cases.

Preliminary results

These data were obtained before and after high dose vitamin C (20-30 per application) treatment (Figure 1). These high-dose vitamin C treatments were performed, 1 or 2times per week (for a total of 10times) or for severe cases, every day of for 10days. The results

show the effects of high dose vitamin C treatment on GOT and GPT even if the interferon treatment was not effective. We describe a 41 year-old man with HBV hepatitis. The serum Glutamic Oxaloacetic Transaminase activity (GOT) and Glutamic Pyruvic Transaminase activity (GPT) were in the range of 300 to 400, and received interferon in a large hospital for 2 years, but there was no improvement. He presented at our hospital in September 1994 and intravenously received 14 high doses (20g) of vitamin C therapy. After 2 months, his data were within the normal range. There has been no exacerbation for 6 years. High-dose vitamin C therapy was very effective for suppressing live inflammation and inhibiting the development of cancer cells (Table 2). High-dose vitamin C (20-30g per dose) was consistently effective for treating hepatitis except for patients who had fulminant hepatitis or autoimmune hepatitis. Patients with fulminant hepatitis required 24-hour intravenous infusion of about 120g of vitamin C. In patients who received detoxification therapy, the effectiveness was evaluated by measuring the following substances after every 3 sessions of treatment: carcinoembryonic antigen (CEA) as an immunosuppressive substance, ferritin as serum protein that stores and release iron, α 1-globulin, and α 2-globulin levels decreased. The immune activity improved after three sessions of detoxification therapy. In addition, the T-cell count increased from 1,252 to 2,184. Detoxification therapy thus enhances immune activity, contributing to the suppression of carcinogenesis in patients with chronic hepatitis. Result of Table 3 provides data for the application of detoxification therapy in a 57-year-old female. □

Table 2 This patient was 41-year-old male suffering from HBV infection. The patient was treated with interferon for 2 years with no effect. He arrived at the hospital in September, 1994 and received high-dose vitamin C treatment for 21 days. After 2 months, his data was within the normal range

	28-Sep	11-Oct	22-Oct	14-Nov	27-Dec	24-Feb
GOT	294	247	187	26	18	25
GPT	323	269	213	25	12	5

Table 3 Detoxification treatment for on a 57-year-old female

Detoxifying therapy:	3 times	3 times	
Date: 1983	5/9	2-Jun	11/4
CEA (ng/ml)	3.1	2.1	1.4
Ferritin (ng/ml)	203	85	60
α 1-globulin (%)	5.7	3	
α 2-globulin (%)	11.9	8.3	
T (%)	73	78	78
T cell number	1252	1460	2184
Stimulation index	165	202	152

The data were measured after every 3time's application of detoxification therapy.

According to the decreasing level of immunosuppressive substances (CEA, ferritin, α -immuno-regulatory protein), the immune activity ranged from 1,252 to 2,184.

Results

The results of 10 year intervention studies using this global strategy to prevent the development of liver cancer in 406 patients are

shown in Table 4. After 10 years, improvement was obtained in 136 patients with F₁ fibrosis and 144 patients with F₂ fibrosis. Among the 49 patients with F₃ fibrosis, improvement was obtained in 34 patients, and 15 patients were unchanged. Among the 77 patients with F₄ fibrosis, 44 patients improved, and 33 patients were unchanged. Over the past ten years, three patients suffered from hepatoma. Thus, liver cancer suffering rate was 0.7% (3/406) (Table 4).

Table 4 Platelet number is classified by fibrotic degree as follows:

Prognosis	Pt number	better change	no change	aggravation
Chronic hepatitis classification				
F₁	136	136		
F₂	144	144		
F₃	49	34	15	
F₄	77	44	33	3

F₁: $18 \times 10^4 / 1 \text{mm}^3 >$, F₂: $15 \times 10^4 / 1 \text{mm}^3 >$, F₃: $13 \times 10^4 / 1 \text{mm}^3 >$, F₄: $10 \times 10^4 / 1 \text{mm}^3 >$

Discussion

Fibrosis in patients with chronic viral hepatitis is associated with decreased vitamin A levels in serum. Patients thus require vitamin A supplementation. Patients with liver fibrosis should also receive branched-chain amino acid granules and vitamin K. In patients with immuno suppression, detoxification therapy as part of the global treatment strategy is thought to have inhibited the exacerbation of chronic hepatitis and the development of liver cancer. Although improvement was not obtained in all patients, we believe that our results showed that three sessions of proactive prophylactic therapy were an effective intervention. Recently, Kanto et al.¹⁹ reported that immune therapy by the transfusion of dendritic cells prevents the development of liver cancer, indicating that the prevention of immuno suppression is important. Because chronic hepatitis is a type of latent infection,²⁰ cold beverage consumption and mouth breathing must be avoided. Moreover, even if HBe antibodies become positive, the process of hepatitis continues, and interferon is often ineffective. In Japan, about 70% of viral hepatitis cases by HCV, and a high proportion of HCV infections are genotype 1b. Interferon is thus often ineffective.²¹⁻²⁵ In the present study, we did not use interferon or oligo nucleotide preparations. Basically, 85 % to 90% of hepatic viral infections are spontaneously cured by sero conversion. It is therefore, important to develop methods for enhancing immunity and thereby prevent the development of liver cancer.

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Conflict of interest

Author declares that there is no conflict of interest.

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