Efficacy of Interferon Treatment on Incidence of Hepatocellular Carcinoma in Patients with Chronic Hepatitis C

〈Original Article〉

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ABSTRACT

To evaluate the effect of interferon (IFN) therapy on the development of hepatocellular carcinoma (HCC) and the risk factors for HCC after treatment, we retrospectively studied 193 patients with chronic hepatitis C who were treated with IFN. Among these patients, the development of HCC was observed in 1 (1.3%) of 74 sustained responders (SR), in 3 (4.5%) of 66 transient responders (TR), and in 10 (18.9%) of 53 non-responders (NR). The cumulative incidence of HCC in SR, TR and NR was predicted to be 1.3%, 3.0%, and 17.0%, respectively, at the fifth year by Kaplan-Meiyer methods, and the annual incidence of HCC was 0.2% in SR, 0.9% in TR, and 3.4% in NR. The development of HCC was significantly reduced not only in SR including patients with incomplete eradication of hepatitis C virus (HCV), but also in TR compared with in NR (NR vs. SR; $p < 0.001$, NR vs. TR; $p = 0.020$). According to the liver histology, the cumulative incidence of HCC in patients with CAH2A and CAH2B was predicted to be 1.5% and 15.6%, respectively, at the fifth year, and the patients with CAH2B had a significantly higher hepatocarcinogenesis than those with CAH2A ($p < 0.001$). As independent risk factors for HCC, the response to IFN ($p = 0.009$) and liver histology ($p = 0.002$) were identified by Cox proportional hazard regression analysis. These results indicate that IFN therapy seems to prevent the risk for HCC in patients with chronic hepatitis C, and that reduction of the histological progression may contribute to decreasing the incidence of HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common carcinomas in the oriental countries (OKUDA, 1992). Most of the cases with HCC are associated with chronic liver disease commonly related to persistent infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) (TAKANO et al, 1995). In Japan, chronic HCV infection is the most important problem in hepatocarcinogenesis, because about 80% of the patients with HCC concomitantly have associated liver cirrhosis related to HCV infection (NISHIOKA et al, 1991; TSUKUMA et al, 1993; SHIRATORI et al, 1995). Some studies on the prognosis of chronic hepatitis C suggest that chronic hepatitis C progresses slowly and often leads to cirrhosis and HCC (SEEFF, 1995). Therefore, the long-term outcome of the patients with chronic HCV infection mainly depends on how the development of HCC can be reduced.

A long-term follow-up study showed that it might take about 20 to 30 years after HCV infection for liver cirrhosis and HCC to develop (KIYOSAWA et al, 1990). However, the actual mechanism of development of HCC by HCV infection is still obscure, and it has been suggested that the increase of genetic alteration caused by continuous damage and replication of hepatocytes possibly lead to the development of HCC.

Interferon (IFN) is currently the only effective agent against HCV infection and has been widely used for treatment of chronic hepatitis C patients (HOOFNAGLE et al, 1997). Many investigators have reported the efficacy of IFN treatment for chronic hepatitis C. Normalization of serum alanine aminotransferase (ALT) levels and clearance of serum HCV RNA were achieved in 15% to 35% of the patients treated with IFN respectively (DAVIS et al, 1989; DI BISCEGLIE et al, 1989; SHINDO et al, 1992; HAGIWARA et al, 1996; SHIRATORI et al, 1997), and histological improvement of inflammation and necrosis of hepatocytes were also reported (POYNARD et al, 1996; TERAMURA et al, 1997).

At the hepatology unit in the First Department of Internal Medicine of Osaka Medical College Hospital, IFN therapy for chronic hepatitis C was started from February 1992, and many patients have received this treatment. The ultimate goal of IFN therapy is eradication of the serum HCV RNA, inhibition of the progression to cirrhosis, and finally reduction of the incidence of HCC. Recently, some investigators have reported that IFN therapy may decrease the risk for HCC in patients with chronic hepatitis C (NISHIGUCHI et al, 1995; IMAI et al, 1998; KASAHARA et al, 1998; SHINDO et al, 1999; OKANOUE et al, 1999; YOSHIDA et al, 1999). These reports suggested that IFN therapy could play an important role in improvement of the prognosis of patients with chronic HCV infection.

In the present study, we evaluated retrospectively the influence of IFN response on the development of HCC and the risk factors for HCC after IFN treatment in patients with chronic hepatitis C.

PATIENTS and METHODS

Patients

From February 1992 to December 1999, a total of 234 patients diagnosed as having chronic hepatitis C were treated with IFN using our standard schedule (intramuscular or intravenous injection every day for the initial 4 weeks and then 3 times a week during the following 20 weeks) at our hepatology unit. Among these patients, 193 patients received IFN therapy between February 1992 and December 1996, who could be followed up for at least 36 months after the cessation of IFN treatment, were enrolled in this study.

All patients had abnormal ALT levels for at least 6 months and were seropositive for the second- or third-generation assay of anti-HCV (Ortho Diagnostics, Tokyo, Japan) and serum HCV RNA before IFN therapy. The diagnosis of chronic hepatitis was based on the histological findings of liver biopsy specimens. Patients who were positive for surface antigen of HBV (HBsAg) or who had an evidence of other forms of liver disease, such as autoimmune hepatitis and alcoholic liver disease, were excluded from this study. Patients who were diagnosed as having liver cirrhosis histologically and clinically using radiological imaging procedures, were also excluded.

The biochemical liver function tests were performed before IFN therapy. In most patients, the level of serum HCV RNA and HCV RNA genotype were determined before starting IFN therapy. There was no evidence of HCC in any patients upon starting this study. The absence of HCC before the start of IFN was assessed by ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI).

HCV RNA levels and HCV genotype assay

The serum HCV RNA levels were quantified by widely used assays, such as the branched DNA

probe assay (version 1; Chiron, Dai-ichi Kagaku, Tokyo, Japan) (LAU ET AL,1993), competitive reverse transcription-polymerase chain reaction (RT-PCR) (Chiron) (KATO et al, 1993), or a combined RT-PCR assay (Amplicor-HCV monitor assay) (SHIRATORI et al, 1997).

Because the serum HCV RNA of 10^5 copies/ml by the combined RT-PCR assay was demonstrated to be equal to approximately 10^6 equivalents/ml assayed by the branched DNA probe assay (SHIRATORI et al, 1997), a low viral level was defined when the serum HCV RNA level was less than 10^6 equivalents/ml by the branched DNA probe method, less than 10^6 copies/ml by the competitive RT-PCR method, or less than 10^5 copies/ml by the combined RT-PCR method.

HCV RNA genotype was determined by genotype-specific primers (OKAMOTO et al, 1992) or by serological grouping of the serum antibodies (TANAKA et al,1994). In this study, genotypes 1a and 1b corresponded to serologic group 1 (Group 1), and genotypes 2a and 2b corresponded to serological group 2 (Group 2).

Liver histology

All patients underwent liver biopsy within 6 months before IFN therapy. The diagnosis of liver biopsy was based on the European classification (DE GROOTE et al, 1968) as follows: chronic persistent hepatitis (CPH), moderate chronic aggressive hepatitis (CAH 2A), severe chronic aggressive hepatitis (CAH 2B), and liver cirrhosis (LC). Each biopsy specimen was also evaluated using the histologic activity index (HAI) described by Knodell et al. (KNODELL et al, 1981) and was scored for the stage of liver fibrosis and grade of inflammatory activity according to the classification of Desmet et al. (DESMET et al, 1994).

IFN treatment schedules and response to IFN therapy

In principle, the standard schedule of IFN therapy in our hepatology unit was daily injection of IFN alpha or beta for the initial 4 weeks and then 3 times a week during the following 20 weeks. However, the administered dose or duration of IFN was changed when severe side effects such as marked leukopenia, thrombocytopenia, psychosis, ophthalmic symptoms or thyroid dysfunction were noticed during IFN therapy. In all patients, the total administered dose of IFN and the total duration of IFN treatment for each patient were at least more than 150 million units (MU) and for more than 4 weeks, respectively. Of the 193 patients, 48 patients were treated with natural IFN alfa (Sumiferon; Sumitomo Pharmaceutical Co., Osaka, Japan) at a dose of 6 MU intramuscularly, 40 patients received recombinant IFN alfa -2a (Canferon; Takeda Chemical Industries Co., Osaka, Japan) at a dose of 9 MU intramuscularly, 87 patients received recombinant IFN alfa-2b (Intron A; Schering-Plough Co., Osaka, Japan) at a dose of 10 MU intramuscularly, and 18 patients received natural IFN beta (Feron; Toray Industries, Tokyo, Japan) at a dose of 6 MU by intravenous injection.

According to the response to IFN therapy, the patients were divided into the following three groups based on the change in the serum ALT level. Sustained responders (SR) were defined as patients whose serum ALT level became normal during therapy and who sustained the normal level for more than 6 months thereafter. Transient responders (TR) were defined as patients whose ALT levels became normal during therapy but increased again within 6 months after completion of the treatment. Non-responders (NR) were defined as patients whose ALT level did not normalized during therapy.

Follow-up after IFN therapy

The patients were enrolled after cessation of IFN treatment and the end of observation was December 1999 or the first day when HCC was detected. All patients were followed carefully to check HCC for more than 3 years after IFN treatment by biochemical examinations and serum tumor markers including alpha fetoprotein (AFP) and protein induced by vitamin K antagonist II (PIVKA-II) every 1 or 2 months and by US approximately every 3 to 6 months. If HCC was detected or suspected, CT, MRI, and hepatic arteriography were performed. The diagnosis of HCC was made on the basis of radiological findings of typical characteristics of HCC and/or typical histological findings by fine-needle aspiration biopsy.

Statistical analysis

The continuous variables were compared using the one-way analysis of variance (ANOVA), and the proportions were compared using x^2 method. The probability of development of HCC was calculated from a period between the end of IFN therapy and the development of HCC, using the Kaplan-Meier method and was compared using the log rank test. The independent factors for the development of HCC were estimated using by Cox proportional hazard analysis. As potential risk factors,

the age, gender, serum HCV RNA level, HCV serological genotype, total administrated dosage of IFN, response to IFN therapy, and histological finding of liver biopsy were used for analysis. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

Patients characteristics and response to IFN therapy

Among 193 patients, a sustained response was found in 74 patients (38%), a transient response in 66 patients (34%), and no response in 53 patients (28%). On the basis of the response to IFN therapy, the baseline characteristics of patients enrolled in this study are shown in **Table 1**.

There were no significant differences in the age ($p = 0.167$), gender ($p = 0.586$), HCV RNA level ($p = 0.340$), total dosage of administered IFN ($p = 0.156$), and median observation period ($p = 0.079$), but there were significant differences in HCV serological genotype ($p = 0.0043$) and liver histology ($p < 0.001$) among SR,TR and NR.

According to the liver histology, most patients with CAH2A corresponded to the patients with less advanced liver fibrosis (F0 or F1) and mild activity, and most patients with CAH2B corresponded to those with stage F2 or F3 fibrosis and severe activity. NR was more frequently found in patients with CAH2B (almost equal to the histologically progressive stage).

Incidence of hepatocellular carcinoma

The mean observation period was 66 months after IFN therapy. During the observation period, HCC was found in 14 patients (12 males and 2 females) after IFN therapy (**Table 2**). Development of HCC was observed in 1 of 74 SR (1.3%), in 3 of 66 TR (4.5%), and in 10 of 53 NR (18.9%). HCC was detected in one patient within 12 months after the end of IFN treatment. There was no development of HCC in any patients who remained viremic after sustained biochemical response to IFN therapy. HCC developed in one

Table 1 Clinical Characteristics in Chronic Hepatitis C Patients According to ALT Response to IFN Therapy

	Sustained responders	Transient responders	Non Responders
Number of patients	74	66	53
Age (years old) *	51 ± 11	51 ± 12	54 ± 10
Male / Female	48 / 26	40 / 26	37 / 16
HCV RNA level (Kcopies/mL)			
≦100	11	6	6
>100	24	32	23
N.T.	39	28	24
HCV selorogical genotype			
Group 1	31	36	32
Group 2	15	5	2
N.T.	28	25	19
Total dosage of IFN (million unit)			
≦ 300	8	6	10
> 300	66	60	43
Liver histology			
CAH2A	57	54	19
CAH2B	17	12	34
Periods of observation (months) *	70 ± 18	63 ± 20	65 ± 22

N.T.; not tested, IFN; interferon
CAH2A; chronic aggressive hepatitis 2A, CAH2B; chronic aggressive hepatitis 2B
* Mean ± SD

Table 2 Characteristics of Chronic Hepatitis C Patients with Development of Hepatocellular Carcinoma after IFN Therapy

Patient No.	Age (yrs)	Gender M/F	HCV Genotype	HCV RNA level (Kcopies/mL)	IFN Type	IFN Dosage (million unit)	Liver Histology	Response to IFN	Follow-up periods (months)
1	49	M	Group 1	N.T.	r- α 2b	280	CAH2A	SR	46
2	60	M	Group 1	N.T.	r- α 2b	880	CAH2B	TR	11
3	60	M	Group 1	360	r- α 2b	880	CAH2A	TR	44
4	58	M	Group 1	2600	r- α 2b	880	CAH2A	TR	67
5	49	M	Group 1	76	r- α 2b	520	CAH2B	NR	18
6	70	F	Group 1	48	n- α	204	CAH2B	NR	26
7	59	M	N.T.	N.T.	n- α	456	CAH2B	NR	28
8	58	M	Group 1	420	r- α 2b	264	CAH2B	NR	28
9	43	M	N.T.	N.T.	r- α 2a	792	CAH2B	NR	35
10	65	M	Group 1	N.T.	n- α	258	CAH2B	NR	50
11	56	M	Group 1	940	n- α	528	CAH2B	NR	53
12	56	M	Group 1	N.T.	r- α 2a	684	CAH2B	NR	54
13	42	M	Group 1	N.T.	n- α	528	CAH2B	NR	56
14	56	F	Group 1	N.T.	n- α	314	CAH2B	NR	68

N.T.; not tested, IFN; interferon, SR; Sustained responder, TR; Transient responder, NR; Non Responders
CAH2A; chronic aggressive hepatitis 2A, CAH2B; chronic aggressive hepatitis 2B

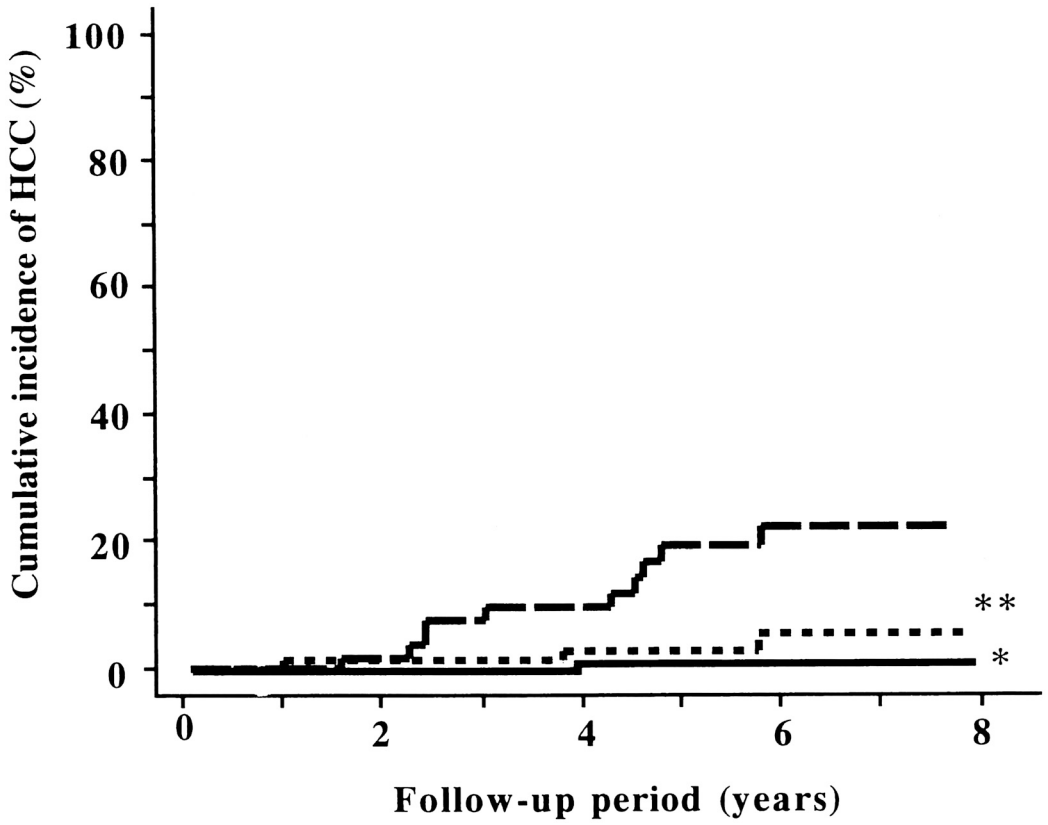

Fig. 1 Cumulative incidence of HCC in chronic hepatitis C patients according to response to IFN therapy. A log-rank test of the three curves of SR (solid line), TR (dotted line) and NR (dashed line) showed a significant difference among three groups (*$p < 0.001$ vs. NR, **$p = 0.020$ vs. NR).

SR and his serum HCV RNA was undetectable at the time of HCC diagnosis. A small-sized HCC was detected in this patient during observation at about 4 years after IFN therapy, and he was cured by surgical treatment.

The incidence of HCC was analyzed in patients with HCV serological group 1 (all patients were tested) or CAH2B (79%). Because most patients with CAH2B corresponded to those with advanced liver fibrosis (F2 or F3) and those with CAH2A corresponded to patients with F0, F1 or F2 stage, HCC mainly developed in patients with advanced fibrosis.

Cumulative incidence of hepatocellular carcinoma

The cumulative incidence of HCC in patients treated with IFN as analyzed by Kaplan-Meiyer method is shown in **Fig. 1** according to the response to IFN therapy. The cumulative incidence of HCC in NR was significantly higher than that in SR (NR vs. SR; $p<0.001$), and in TR (NR vs. TR; $p=0.020$). The third-year incidence of HCC in SR, TR, and NR were predicted to be 0%, 1.6%, and 9.4%; and the fifth-year incidence to be 1.3%, 3.0%, and 17.0%, respectively.

Because the patients treated with IFN had different clinical characteristics especially in the histological activity or fibrosis, the cumulative incidence of HCC was estimated with respect to the histological findings of liver biopsy (**Fig. 2**). The patients with advanced stage (CAH2B) had a significantly higher incidence of HCC than those with less advanced stage (CAH2A) ($p<0.001$). The cumulative incidence of HCC in patients with CAH2A and CAH2B was predicted to be 0% and 9.4% at the third year, and 1.5% and 15.6% at the fifth year, respectively.

Annual incidence of hepatocellular carcinoma

The annual incidence of HCC in chronic hepatitis C after IFN therapy was 0.2% in SR, 0.9% in TR, and 3.4% in NR by the person-years method according to IFN response. The annual incidence was especially lower in SR, but it increased to

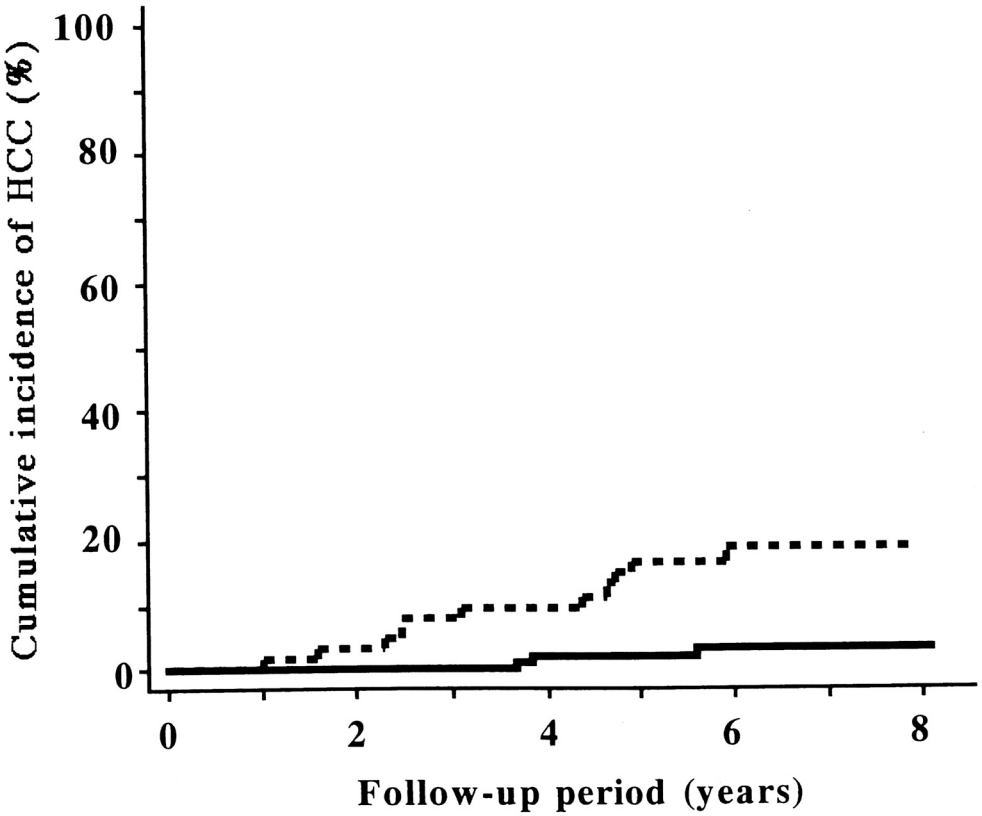

Fig. 2 Cumulative incidence of HCC in chronic hepatitis C patients treated with IFN according to liver histology. A log-rank test of the two curves of patients with CAH 2A (solid line) and CAH 2B (dotted line) showed a significant difference between two groups ($p<0.001$).

3.4% in NR.

Factors contributing to development of hepatocellular carcinoma

To identify the risk factors affecting the incidence of HCC, the age (older than 60 years), gender (male), serum HCV RNA level (low viral level), HCV serological group (Group 1), total IFN dosage (less than 300 MU), response to IFN therapy (SR), liver histology (CAH2A) were analyzed using Cox proportional hazards regression method. The response to IFN ($p = 0.009$) and liver histology ($p = 0.002$) were identified as independent risk factors associated with the incidence of HCC (**Table 3**). The risk of HCC in patients without viral eradication and/or normalization of serum ALT level was 15.79 times higher (95% CI, $p = 0.001$) than in SR. The patients with histologically advanced stage (CAH2B) had a significantly higher risk ratio (risk ratio, 7.80; 95% CI, $p = 0.001$) than those with less advanced stage (CAH2A). The age, gender, HCV RNA levels, HCV serotype, and total IFN dosage did not influence the development of HCC in the present study.

DISCUSSION

In this study, we demonstrated that the development of hepatocellular carcinoma was significantly lower in patients with HCV eradication and/or ALT normalization by IFN therapy than in NR. This result suggests that IFN treatment, at least in SR, may reduce the risk for the development of HCC in chronic hepatitis C patients.

Regarding the mechanism of carcinogenesis, it has been suggested that mutational activation of an oncogene coupled with loss of several genes that normally suppress carcinogenesis (VOGELSTEIN et al, 1988) are needed for the development of cancer. However, the actual mechanisms of hepatocarcinogenesis are still unknown in patients with HCV infection, HCC is considered to result from a series of genetic alterations leading to continuous inflammation, hepatocyte necrosis, cell damage and regeneration.

The development of HCC was significantly reduced not only in SR including patients with the complete eradication of HCV, but also in TR in the

Table 3 Risk Factors for the Development of Hepatocellular Carcinoma in Patients with Chronic Hepatitis C after IFN Therapy

Variables	Risk Ratio (95% CI)	P Value
Age (years)		
< 60	1.0	0.404
$\geqq 60$	0.53 (0.12 - 2.36)	
Gender		
Male	1.0	0.121
Female	0.31 (0.07 - 1.37)	
HCV RNA level (Kcopies/mL)		
$\leqq 100$	1.0	0.519
> 100	0.61 (0.14 - 0.27)	
HCV serological genotype		
Group 1	1.0	0.403
Others	0.82 (0.51 - 1.32)	
Total IFN dosage (million unit)		
< 300	1.0	0.082
$\geqq 300$	0.36 (0.11 - 1.14)	
Response to IFN		
Sustained response	1.0	0.009
Non response	15.79 (2.02 - 123.47)	
Liver Histology		
CAH2A	1.0	0.002
CAH2B	7.80 (2.17 - 27.95)	

present study. However, the cumulative incidence of HCC in TR was gradually increased after years in comparison with that in SR. These results suggested that the effects of IFN which included activation of the cytotoxic T cells (CHEN et al, 1986) and natural killer cells (SWAMINATHAN et al, 1992), inhibition of cell growth and division (HARADA et al, 1993; HANNIGAN et al, 1990), and reduction of necro-inflammation in the liver, may stop the steps of hepatocarcinogenesis and prevent or delay the appearance of HCC. Some reports indicated that activated necro-inflammation of hepatocytes was a high risk for HCC development in patients with HCV-associated cirrhosis, suggesting the importance of the hepatocellular proliferation and inflammatory necrosis in hepatocarcinogenesis (TARAO et al, 1994). Concerning the possibility of preventing or delaying the development of HCC by reducing the hepatic necro-inflammation and maintaining the serum ALT at low level, it is thought to be clinically important to try IFN therapy for patients with chronic hepatitis C, even if HCV is not eradicated.

In the present investigation, the cumulative incidence of HCC in NR was significantly higher than that in SR or TR, and the third-year and the fifth-year incidence of HCC were predicted to be 9.4% and 17.0%, respectively. The annual incidence of HCC after IFN therapy was 3.4%. Because the number of patients without any treatment was too small to be considered as proper controls, there were not control patients in the present study. In addition, the present study was not a randomized controlled study but a retrospective one, so it was unknown whether IFN can reduce the risk for HCC especially in NR. Some previous studies have reported that the development rate of HCC is approximately 1 to 3% during the natural course of chronic hepatitis C (TAKANO et al, 1995; IKEDA et al, 1993), and the third-year and the fifth-year incidence of HCC in the untreated patients were 5 to 8% and 13 to 15%, respectively (YOSHIDA et al, 1999; IMAI et al, 1998). Therefore, the incidence of HCC in NR was assumed to be almost equal to that of non-treated patients with chronic hepatitis C. These results suggested that other treatments would be needed for chronic hepatitis C patients with no response to IFN therapy to prevent the development of HCC.

Generally, the incidence of HCC in SR is rare. In our study, the development of HCC was found after IFN treatment in one SR case with complete eradication of HCV by IFN therapy. In most reported cases who developed HCC, cancer was found within 4 to 5 years after IFN therapy and their histological findings were indicated an advanced fibrotic stage. Thus, even if IFN is effective for normalization of ALT level and eradication of HCV, the patients with histologically advanced stage should undergo carefull follow-up for at least 5 years after IFN therapy to prevent development of HCC.

Several studies showed that older age, male, HCV serological genotype 1, non-response to IFN therapy, and histologically advanced stage were high risk factors for HCC (IKEDA et al, 1993; TSUKUMA et al, 1993; BRUNO et al, 1997, IMAI et al, 1998; KASAHARA et al, 1998; SHINDO et al, 1999; YOSHIDA et al, 1999; OKANOUE et al, 1999). The present study showed that response to IFN and liver histology were independent factors for develpoment of HCC.

According to the response to IFN therapy, NR was identified as one of the independent factors for the development of HCC. In the patients treated with IFN, the response to IFN would closely correlated with several clinical characteristics before IFN therapy. Many studies have indicated that chronic hepatitis C patients with several factors such as insufficient dose or period of IFN administration, HCV serological subtype 1, high serum HCV RNA levels or histologically advanced stage were difficult to treat effectively (POYNARD et al, 1996; HOOFNAGLE et al, 1997; CAMMA et al, 1997; SHIRATORI et al, 1997). The patients with these factors are predicted to be NR before IFN treatment, and therefore they need more effective anti-viral therapy or other treatments for suppressing the persistent inflammation and necrosis of hepatocytes to prevent development of cirrhosis or HCC.

Our analysis showed that the liver histology also was identified as an independent risk factor for HCC. In the present investigation, most patients with HCC detected after IFN had histologically diagnosed CAH2B before IFN therapy. Recently, several reports have indicated that the degree of liver fibrosis is the most important risk factor for development of HCC (IMAI et al, 1998; OKANOUE et al, 1999; SHINDO et al, 1999; YOSHIDA et al, 1999). In HCV-related cirrhosis in Japan, the annual incidence of HCC is 5 - 7% (OKA et al, 1990; IKEDA et al, 1993; KATO et al, 1994). Thus, patients with histologically advanced stage should be regarded as a high risk group for development of HCC. Especially, in chronic hepatitis C patients with histologically advanced

stage and severe activity as well as with non-response to IFN therapy, careful management and regular check of the serum tumor markers and imaging studies including US and CT should be done to detect HCC as early as possible.

In conclusion, the risk for incidence of HCC was significantly reduced in patients who showed sustained normalization of the serum ALT with or without eradication of the serum HCV RNA by IFN therapy. Our results suggest that IFN therapy seems to reduce the risk for HCC in patients with chronic hepatitis C, and reduction of the hepatocytes inflammation and histological progression may contribute to decreasing the incidence of HCC.

REFERENCES

BRUNO S, SILINI E, CROSIGNANI A, BORZIO F, LEANDRO G, BONO F, ASTI M, ROSSI S, LARGHI A, CERINO A, PODDA M, MONDELLIM U : Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. Hepatology 25 : 754-758, 1997

CAMMA C, GIUNTA M, LINEA C, PAGLIARO L : The effect of interferon on the liver in chronic hepatitis C:a quantitative evaluation of histology by meta-analysis. J Hepatol 26 : 1187 - 1199, 1997

CHEN LK, TOURVIEILLE B, BURNS GF, BACH FH, MATHIEU MAHUL D, SASPORTES M, BENSUSSAN A : Interferon:a cytotoxic T lymphocyte differentiation signal. Eur J Immunol 16 : 767-770, 1986

DAVIS GL, BALART LA, SCHIFF ER, LINDSAY K, BODENHEIMER HC JR, PERRILLO RP, CAREY W, JACOBSON IM, PAYNE J, DIENSTAG JL, DAVID H, VAN THIEL, TAMBURRO C, LEFKOWITCH J, ALBRECHT J, MESCHIEVITZ C, ORTEGO TJ, GIBAS A : Treatment of chronic hepatitis C with recombinant interferon alfa.A multicenter randomized, controlled trial. N Engl J Med 321 : 1501-6, 1989

DE GROOTE J, DESMET VJ, GEDIGK P, KORB G, POPPER H, POULSEN H, SCHEUER PJ, SCHMID M, THALER H, UEHLINGER E : A classification of chronic hepatitis. Lancet II : 626, 1968

DESMET VJ, GERBER M, HOOFNAGLE JH, MANNS M, SCHEUER PJ : Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 19 : 1513-20, 1994

DI BISCEGLIE AM, MARTIN P, KASSIANIIDES C, LISKER-MELMAN M, MURRAY L, WAGGONER J, GOODMAN Z, BANKS SM, HOOFNAGLE JH : Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. N Engl J Med 321 : 1506-10, 1989

HAGIWARA H, HAYASHI N, KASAHARA A, OSHITA M, KATAYAMA K, NAITO M, MASUZAWA M, YOSHIHARA H, SHIMIZU Y, FUSAMOTO H, KAMADA T : Long-term biochemical and virological response to natural interferon-alpha in patients with chronic hepatitis C. Dig Dis Sci 41 : 1001-1107, 1996

HANNIGAN GE, WILLIAMS BRG : Signal trnsduction by interferon-alpha through arachidonic acid metabolism. Science 251 : 204-207, 1990

HARADA H, KITAGAWA M, TANAKA N, YAMAMOTO H, HARADA K, ISHIHARA M, TANIGUCHI T : Anti-oncogenic and oncogenic potetials of interferon regulatory factors-1 and -2. Science 259 : 971-974, 1993

HOOFNAGLE JH, DI BISCEGLIE AM : The treatment of chronic viral hepatitis. N Engl J Med 336 : 347 - 356, 1997

IKEDA K, SAITOH S, ARASE Y, CHAYAMA K, SUZUKI Y, KOBAYASHI M, TSUBOTA A, KOBAYASHI M, NAKAMURA I, MURASHIMA N, KUMADA H, KAWANISHI M : Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1643 patients using statistical bias correction with proportional hazard analysis. Hepatology 29 : 1124-1130, 1999

IKEDA K, SAITOH S, KOIDA I, ARASE Y, TSUBOTA A, CHAYAMA K, KUMADA H, KAWANISHI M : A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with vral and alcholic cirrhosis. Hepatology 18 : 47-53, 1993

IMAI Y, KAWATA S, TAMURA S, YABUUCHI I, NODA S, INADA M, MAEDA Y, SHIRAI Y, FUKUZAKI T, KAJI I, ISHIKAWA H, MATSUDA Y, NISHIKAWA M, SEKI K, MATSUZAWA Y : Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Ann Intern Med 129 : 94-99, 1998;

KASAHARA A, HAYASHI N, MOCHIZUKI K, TAKAYANAGI K, KAKUMU S, IIJIMA A, URUSHIHARA A, KIYOSAWA K, OKUDA M, HINO K, OKITA K : Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Hepatology 27 : 1394-1402, 1998

KATO Y, NAKATA K, OMAGARI K, FURUKAWA R, KUSUMOTO Y, MORI I, TAJIMA H, TANIOKA H, YANO M, NAGATAKI S : Risk of hepatocellular carcinoma in patients with cirrhosis in Japan.

Cancer 74 : 2234-2238, 1994

KATO N, YOKOSUKA O, HOSODA K, ITO Y, OHTO M, OMATA M : Quantification of hepatitis C virus by competitive reverse transcription-polymerase chain reaction. Hepatology 18 : 16-20, 1993

KIYOSAWA K, SODAYAMA T, TANAKA E, GIBO Y, YOSHIZAWA K, NAKANO Y, FURUTA S, AKAHANE Y, NISHIOKA K, ROBERT H, HARVEY J : Interrelationship of blood transfusion,non-A,non-B hepatitis and hepatocellular carcinoma.Analysis by detection of antibody to hepatitis C virus. Hepatology 12 : 671-675, 1990

KNODELL RG, ISHACK KG, BLAACK WC, CHEN TS, CRAIG R, KAPLOWITZ N, KIERNAN TW : Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1 : 431-435, 1981

LAU JYN, DAVIS GL, KNIFFEN J, QIAN KP, URDEA MS, CHAN CS, MIZOKAMI M, NEUWALD PD, WILBER JC : Significance of serum hepatitis C virus RNA levels in chronic Hepatitis C. Lancet 341 : 1501-1504, 1993

NISHIGUCHI S, KUROKI T, NAKATANI S, MORIMOTO H, TAKEDA T, NAKAJIMA S, SHIOMI S, SEKI S, KOBAYASHI K OTANI S : Randomised trial of effect of interferon-α on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 346 : 1051 - 1055, 1995

NISHIOKA K, WATANABE J, FURUTA S, TANAKA E, IINO S, SUZUKI H, TSUJI T, YANO M, KUO G, CHOO QL, HOUGHTON M, ODA T : A high prevalence of antibody to the patients C virus in patients with hepatocellular carcinoma in Japan. Cancer 67 : 429-433, 1991

OKA H, KURIOKA N, KIM K, KANNO T, KUROKI T, MIZOGUCHI Y, KOBAYASHI K : Prospective study of early detection of hepatocellular carcinoma in patients with cirrhosis. Hepatology 12 : 680-687, 1990

OKAMOTO H, SUGIYAMA Y, OKADA S, KURAI K, AKAHANE Y, SUGAI Y, TANAKA T, SATO K, TSUDA F, MIYAKAWA Y, MAYUMI M : Typing hepatitis C virus by polymerase chain reaction with type-specific primers: application to clinical surveys and tracing infectious sources. J Gen Virol 73 : 673-679, 1992

OKANOUE T, ITOH Y, MINAMI M, SAKAMOTO S, YASUI K, SAKAMOTO M, NISHIOJI K, MURAKAMI Y, KASHIMA K : Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage:a retrospective study in 1148 patients. J Hepatology 30 : 653-659, 1999

OKUDA K : Hepatoccellularcarcinoma: recent progress. Hepatology 15 : 948-63, 1992

POYNARD T, LEROY V, COHARD M,THEVENOT T, MUTHURIN P, OPOLON P, ZARSKI JP : Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 24 : 778-89, 1996

SEEFF LB : Hepatitis C. Semin Liver Dis 15 : 1-109, 1995.

SHINDO M, ARAI K, OKUNO T : Varying incidence of cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis C responding differently to interferon therapy. Cancer 85 : 1943-1950, 1999

SHINDO M, DI BISCEGLIE AM, HOOFNAGLE JH : Long-term follow-up of patients with chronic hepatitis C treated with α -interferon. Hepatology 15 : 1013-1016, 1992

SHIRATORI Y, KATO N, YOKOSUKA O, IMAZEKI F, HASHIMOTO E, HAYASHI N, NAKAMURA A, ASADA M, KURODA H, TANAKA N, ARAKAWA Y, OMATA M : Predictors of the efficacy of interferon therapy in chronic hepatitis C virus infection. Gastroenterology 113 : 558 - 566, 1997

SHIRATORI Y, SHIINA S, IMAMURA M, KATO N, KANAI F, OKUDAIRA T, TERATANI T, TOHGO F, TODA N, OHASHI M, OGURA K, NIWA Y, KAWABE T, OMATA M : Characteristic difference of hepatocellular carcinoma between hepatitis B- nad C- viral infection in Japan. Hepatology 22 : 1027-1033, 1995

SWAMINATHAN N, LAI CM, BEILHARZ MW, BOYER SJ, KLINKEN SP : Biological activities of recombinant murine interferons alpha 1 and alpha 4:large difference in antiproliferative effect. Antiviral Res 19 : 149-159, 1992

TAKANO S, YOKOSUKA O, IMAZEKI F, TAGAWA M, OMATA M : Incidence of hepatocellular carcinoma in chronic hepatitis B and C:a prospective study of 251 patients. Hepatology 21 : 650-655, 1995

TANAKA T, TSUKIYAMA K, YAMAGUCHI K, YAGI S, TANAKA S, HASEGAWA A, OHTA Y, HATTORI N, KOHARA M : Significance of specific antibody assay for genotyping of hepatitis C virus. Hepatology 19 : 1347-1353, 1994

TARAO K, OHKAWA S, SHIMIZU A, HARADA M, NAKAMURA Y, ITO Y, TAMAI S, HOSHINO H, INOUE T, KANISAWA M : Significance of hepatocellular proliferation in the development of hepatocellular carcinoma from anti-hepatitis C virus-positive cirrhotic patients. Cancer 73 : 1149-1154, 1994

TERAMURA K, FUKUDA A, KOBAYASHI H, YOSHIMO-

TO S, KAWASHIMA H, OHSAWA N : Virus elimination and histologic improvement in patients with chronic hepatitis C treated with interferon alpha. J Clini Gastroenterol 25 : 346-351, 1997

TSUKUMA H, HIYAMA T, TANAKA S, NAKAO M, YABUUCHI T, KITAMURA T, NAKANISHI K, FUJIMOTO I, INOUE A, YAMAZAKI H, KAWASHIMA T : Risk factors for hepatocellular carcinoma among patients with chronic liver diseases. N Engl J Med 328 : 1797-1801, 1993

VOGELSTEIN B, FEARON ER, HAMILTON SR, KERN SE, PREISINGER AC, LEPPERT M, NAKAMURA Y, WHITE R, SMITS AM, BOS JL : Genetic alteration during colorectal-tumor development. N Engl J Med 319 : 525-532, 1988

YOSHIDA H, SHIRATORI Y, MORIYAMA M, ARAKAWA Y, IDE T, SATA M, INOUE O, YANO M, TANAKA M, FUJIYAMA S, NISHIGUCHI S, KUROKI T, IMAZEKI F, YOKOSUKA O, KINOYAMA S, YAMADA G, OMATA M : Interferon therapy reduces the risk for hepatocellular carcinoma:national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. Ann Intern Med 131 : 174-181, 1999