Interferon Therapy for Hepatitis C Virus (HCV)-related Advanced Chronic Hepatitis after Treatment of Recurrent Hepatocellular Carcinoma: A Successful Case

Yoshikuni KUDO*, ***, Hideo TERAOKA**, Tsuyoshi ARITA*, Hisanori KAWASAKI***, Shunzo SATO*, Hisanori ABE*, Masaaki KODAMA****, Toshio FUJIOKA****, Kazunari MURAKAMI***** and Masaru NASU*****

Abstract

A complete response was obtained by interferon (IFN) therapy for hepatitis C virus (HCV)-related advanced chronic hepatitis after curative treatment of initial and recurrent hepatocellular carcinoma (HCC). The patient is alive 73 months after diagnosis of initial HCC and is in a tumor-free state 53 months after diagnosis of the last HCC. This case suggests that it is possible to suppress recurrence and to prolong the life of patients with HCV-related advanced chronic hepatitis, if a complete response is obtained by means of IFN therapy after the curative treatment of the recurrent HCC.

(Internal Medicine 41: 202–206, 2002)

Key words: readministration of interferon (IFN), complete response, hepatic fibrosis, quality of life (QOL), prognosis

Introduction

A characteristic of hepatocellular carcinoma (HCC) complicated with hepatitis C virus (HCV)-related chronic hepatitis or cirrhosis is that it recurs frequently after curative therapies for the initial HCC (1). Once local recurrence occurs, treatment has usually focused on curing only the recurrent HCC. To our knowledge, only a few reports have been published in the English language literature on the prevention of future HCC recurrence in these patients. We treated a patient whose HCC with HCV-related advanced chronic hepatitis did not recur for a long period following successful interferon (IFN) therapy after curative treatment of recurrent HCC. The results of our case report suggest that, even with HCV-related advanced chronic hepatitis complicated with recurrent HCC, it is possible to prevent recurrence of HCC and to prolong the disease-free inter-

val, thereby improving the quality of life (QOL) of the patient by a well-designed IFN therapy after curative treatment of the recurrent HCC.

Case Report

A 66-year-old man who received contaminated blood transfusion during a pulmonary surgery in 1953, was referred to our institution for examination and treatment for possible chronic hepatitis. The patient denied any drinking habit and any history of weight loss. In August 1990, hepatic dysfunction was noticed during a routine health examination and a diagnosis of HCV-related chronic hepatitis (F2/A2) (2) was made by laparoscopy and liver biopsy was performed the same year.

In April 1995, the first IFN therapy was performed, which led to a transient normalization of serum ALT but not to the elimination of HCV-RNA. In September 1995, an initial HCC, 2.7 cm in diameter, developed in segment seven (S7) of the liver which was cured with percutaneous ethanol injection therapy (PEIT) (Fig. 1A). In June 1996, a recurrent HCC, 2.5 cm in diameter, was observed in segment six (S6) of the liver, which was treated with transcatheter arterial embolization (TAE) and PEIT (Fig. 1B). As the laboratory follow-up examination showed a high level of serum transaminase with fluctuations and a decreased HCV-RNA titer, the patient was readmitted in October 1996 for repeat IFN therapy.

On readmission, the laboratory data showed elevation of serum transaminases and thymol turbidity test (TTT), and a low platelet count. Alpha-fetoprotein (AFP) and protein-induced by vitamin K absence II (PIVKA-II) were normal. Anti-HCV antibody was positive and HCV-RNA titer was less than 0.5 mEq/ml by branched DNA probe assay and less than $1 \times 10^{3.5}$ copies/50 μ l by reverse transcription-polymerase chain reaction (RT-PCR) method (Table 1). Genotype analysis revealed a type 1b. Abdominal computed tomography (CT) scan revealed post-TAE and PEIT lipiodol deposition in S6 and S7, but on the dynamic CT no enhancement lesion was seen, indicating

From *the Arita-Icho Hospital, Oita, **the Health Science Center, Oita University, Oita, ***the Kawasaki Medical Clinic, Oita, ****the Department of General Medicine, Oita Medical University, Oita and *****the Second Department of Internal Medicine, Oita Medical University, Oita

Received for publication June 28, 2001; Accepted for publication November 15, 2001

Reprint requests should be addressed to Dr. Yoshikuni Kudo, the Kawasaki Medical Clinic, 263-1 Furuno, Hasama-machi, Oita-gun, Oita 879-5511

Figure 1. A) Abdominal plain CT scan on October 1995 (i.e. 3 days after PEIT) shows lipiodol deposition in S7 of the liver. B) Abdominal enhanced CT scan on May 1997 (i.e. 11 months after TAE and PEIT) shows lipiodol deposition in S6 of the liver. No enhanced lesion is seen. C) Abdominal plain CT scan on May 1997 (i.e. 1 week after PEIT) shows lipiodol deposition in S3 of the liver.

Table 1. Laboratory Data on Admission (October 1996)

WBC	4,200/mm ³	Blood urea nitrogen	13.9 mg/dl
RBC	404×10 ⁴ /mm ³	Creatinine	1.0 mg/dl
Hb	13.8 g/dl	Fasting blood glucose	95 mg/dl
Hematocrit	38.9%		
Platelets	12.5×10 ⁴ /mm ³	PT	114.2%
		APTT	92.2%
		AT-III	69.9%
Total protein	8.1 g/dl	Anti-HBs	(-)
Albumin	3.5 g/dl	HCVAb (II nd)	(+)
TTT	9.4 U	HCV-RNA	
ZTT	10.7 U	RT-PCR	10 ^{3.5} copies/50 µl
Total bilirubin	1.0 mg/dl	Branched DNA probe assay	<0.5 mEq/ml
AST	95 IU/l	Genotype	1b
ALT	131 IU/l		
LDH	268 IU/l	AFP	10.5 ng/ml
ALP	193 IU/l	PIVKA-II	0.01 mAU/ml
γ-GTP	40 IU/l		
Choline esterase	0.70 ΔpH		
Total cholesterol	173 mg/dl		

TTT: thymol turbidity test, ZTT: zinc sulfate turbidity test, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, PT: prothrombin time, APTT: activated partial thromboplastin time, AT-III: anti-thrombin III, HCV: hepatitis C virus, Ab: antibody, RT-PCR: reverse transcription-polymerase chain reaction, AFP: alpha-fetoprotein, PIVKA-II: protein-induced by vitamin K absence II.

Figure 2. Clinical course.

no recurrence of HCC. The clinical course is shown Fig. 2.

The second IFN therapy was started in October 1996 after providing detailed information with regard to his condition and treatment, and after gaining his informed consent. In addition, a total of 204 MU IFN- β was administered. However, since marked proteinuria was observed, the drug was changed to recombinant IFN- α 2b in December of the same year, which was administered until January 1997, totaling in all 138 MU of IFN- α 2b administered. Serum ALT showed a tendency to decrease after the IFN- α 2b therapy was completed, and it has remained within the normal range since May 1997. HCV-RNA became negative and has continued to be persistently negative. Liver biopsy showed F3/A3 in April 1995 before the initial IFN administration (Fig. 3A), and F3-4/A1 in February 1996 before the second IFN administration (Fig. 3B). The liver histology after complete response was improved both in staging and activity to F2/A0 in June 2000, or 41 months after the completion of the second IFN therapy (Fig. 3C).

In May 1997, 4 months after the second IFN therapy (i.e. 20 months from the initial HCC), a third HCC recurred in segment three (S3) and it was cured by means of another PEIT (Fig. 1C). No further recurrence of HCC has been observed as of October 2001, or 53 months after the diagnosis of the last HCC (i.e. 73 months from the initial HCC, 57 months from the disappearance of HCV).

Discussion

HCC recurs quite frequently after the curative treatment of HCC in patients with HCV-related chronic hepatic diseases (1). Therefore, it is very important to prevent recurrence. Recent studies have shown that IFN therapy is associated with reducing the incidence of HCC in patients with chronic hepatitis C and type C cirrhosis (3, 4). We have also reported previously the results of a case showing the effect of IFN therapy in preventing HCC recurrence (5).

Tarao and colleagues reported earlier that the cumulative rate of HCC complications was higher as the serum transaminase persists at high levels (6). The data in this case indicate that serum transaminase levels also persisted at a high level with multimodal variations even after the curative treatment of HCC, suggesting the possibility of a recurrence of HCC. Hence some measures had to be taken to prevent such a recurrence. Arase et al pointed out that normalization, albeit transient, of serum ALT during IFN therapy and a low viral titer were predictive factors in determining whether readministration of IFN is successful (7). Arase et al also reported that there were patients with HCV-related chronic hepatitis who showed fluctuations in HCV-RNA levels, and that administration of IFN to those patients during the period of a low viral titer often proved to be quite effective (8).

By extrapolating these findings, we considered applying the IFN therapy in the present case study. It was thought that this

Figure 3. A) Liver biopsy specimen taken before first IFN therapy (April 1995). Histopathological examination shows chronic active hepatitis (F3/A3) (Silver stain, $\times 40$). B) Liver biopsy specimen taken before second IFN therapy (February 1996). Histopathological examination shows F3-4/A1 (Silver stain, $\times 40$). C) Liver biopsy specimen taken 41 months after second IFN therapy (June 2000). Remarkable improvement of inflammation and fibrosis is observed (F2/A0) (Silver stain, $\times 40$).

therapy could be quite effective because the initial HCC and the subsequent recurrent HCC had been successfully cured, and the initial IFN therapy has been transiently effective. Also HCV-RNA titer had showed a lower level of $1 \times 10^{3.5}$ copies/50 μ l or less than 0.5 mEq/ml immediately before the second administration. As expected, readministration of IFN elicited a complete response. Furthermore, liver histology revealed an improvement in staging and in activity after the IFN therapy when compared to the images before the therapy. The images were also found to be similar to the case previously reported (9, 10).

HCC developed three times in this patient during the period of 20 months from September 1995 when the initial HCC was observed. At the present time, 53 months have passed since HCC was cured for the third time. The patient is alive and has no tumor conditions and shows a normal level of serum transaminase. The third HCC, which developed 4 months after the completion of the second IFN therapy, was suspected to have been already present, but was undetectable by diagnostic imaging before the IFN therapy. Since there has been no recurrence of HCC for more than 4 years after the treatment of the last HCC, it is suggested that IFN therapy is effective in preventing the recurrence of HCC.

It has been documented that HCC develops as a result of the accumulation of abnormal genes by repeated necrosis and regeneration of hepatocytes caused by inflammation which ac-

companies persistent infection of HCV (11), or by hepatic fibrosis acting as a promoter of liver carcinogenesis (12).

There are some reports showing a reduction of intrahepatic recurrence by IFN therapy after the curative treatment of initial HCC underlying chronic hepatitis C (13, 14). But the studies which show that IFN therapy suppresses further recurrence after the development of repeated HCC are very few. Although the genetic mechanism of IFN therapy in decreasing intrahepatic recurrence is still unknown, the present study suggests clinically that improvement of hepatic necro-inflammation and fibrosis induced by readministration of IFN can lead HCV-related chronic hepatitis after curative treatment of repeated HCC from the hypercarcinogenic state to the hypocarcinogenic state even when the initial IFN therapy was unsuccessful. Therefore, there is evidence to show that even in HCV-related chronic hepatitis with complications of repetitive HCC recurrence such as in the present case, further recurrence of HCC can be suppressed in the long-term by IFN, if HCC is appropriately cured, and if IFN therapy is given in an appropriate regime and the treatment leads to a complete response. Furthermore, the direct antitumor action of IFN may also suppress the growth of occult or undetectable HCC (15).

The results of the present study suggest that IFN therapy is effective in suppressing further recurrence of HCC, improving the QOL and prolonging the life of patients with HCV-related advanced chronic hepatitis with complications of recurrent

HCC. Further studies are recommended to improve treatment of the underlying hepatic disease and to prevent tumor development for a better and more favorable prognosis of HCC patients.

References

- 1) Ikeda K, Saitoh S, Tsubota A, et al. Risk factors for tumor recurrence and prognosis after curative resection of hepatocellular carcinoma. *Cancer* **71**: 19–25, 1993.
- 2) Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* **19**: 1513–1520, 1994.
- 3) Nishiguchi S, Kuroki T, Nakatani S, et al. Randomised trial of effects of interferon- α on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* **346**: 1051–1055, 1995.
- 4) Mazzella G, Accogli E, Sottili S, et al. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. *J Hepatol* **24**: 141–147, 1996.
- 5) Kudo Y, Terao H, Arita T, Sato R, Sonoda Y, Nishizono A. A successful case of interferon therapy for hepatitis C virus-related cirrhosis after treatment of hepatocellular carcinoma. *Acta Hepat Jap* **40**: 608–613, 1999 (in Japanese).
- 6) Tarao K, Takemiya S, Tamai S, et al. Relationship between the recurrence of hepatocellular carcinoma (HCC) and serum alanine aminotransferase levels in hepatectomized patients with hepatitis C virus-associated cirrhosis and HCC. *Cancer* **79**: 688–694, 1997.
- 7) Arase Y, Kumada H, Chayama K, et al. Interferon retreatment of nonresponders with HCV-RNA-positive chronic hepatitis C. *J Gastroenterol* **29**: 299–304, 1994.
- 8) Arase Y, Ikeda K, Chayama K, et al. Fluctuation patterns of HCV-RNA serum level in patients with chronic hepatitis C. *J Gastroenterol* **35**: 221–225, 2000.
- 9) Shiratori Y, Imazeki F, Moriyama M, et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Intern Med* **132**: 517–524, 2000.
- 10) Kudo Y, Terao H, Arita T, Sato R, Nishizono A, Fujioka T. A case of type C cirrhosis with marked improvement of liver fibrosis after interferon therapy. *Acta Hepat Jap* **39**: 255–260, 1998 (in Japanese).
- 11) Ikeda K, Saitoh S, Arase Y, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: A long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology* **29**: 1124–1130, 1999.
- 12) Sakaida I, Hironaka K, Uchida K, Suzuki C, Kayano K, Okita K. Fibrosis accelerates the development of enzyme-altered lesions in the rat liver. *Hepatology* **28**: 1247–1252, 1998.
- 13) Suou T, Mitsuda A, Koda M, et al. Interferon alpha inhibits intrahepatic recurrence in hepatocellular carcinoma with chronic hepatitis C: a pilot study. *Hepatol Res* **20**: 301–311, 2001.
- 14) Ikeda K, Arase Y, Saitoh S, et al. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor —A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* **32**: 228–232, 2000.
- 15) Lai CL, Lau JYN, Wu PC, et al. Recombinant interferon- α in inoperable hepatocellular carcinoma: A randomized controlled trial. *Hepatology* **17**: 389–394, 1993.