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TOPIC HIGHLIGHT

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Secondary prevention of recurrence by interferon therapy after ablation therapy for hepatocellular carcinoma in chronic hepatitis C patients

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Abstract

Chronic hepatitis C is a leading cause of hepatocellular carcinoma (HCC) worldwide. Interferon (IFN) therapy decreases the incidence of HCC in patients with chronic hepatitis C. Prevention of chronic-hepatitis-C-related HCC is one of the most important issues in current hepatology. We have previously reported that male gender and high titer of hepatitis C virus (HCV) RNA are predictive factors for the development of HCC in HCV-related cirrhosis. Clinical efforts at eradicating or reducing the viral load may reduce the risk for HCC. Furthermore, because HCC often recurs after ablation therapy, we performed a trial of IFN in patients with chronic liver disease caused by HCV to see whether IFN therapy decreases recurrence after ablation therapy of HCV-related HCC. By using IFN therapy as a secondary prevention, patients with HCC who had received complete tumor ablation showed better survival, primarily as a result of the preservation of liver function and also probably prevention of recurrence. Postoperative IFN therapy appears to decrease recurrence after ablation therapy such as radiofrequency ablation (RFA) therapy of HCV-related HCC. We believe that there is a survival benefit in secondary prevention using IFN therapy. However, a controlled study is essential to obtain conclusive evidence of the efficacy of this strategy.

Key words: Hepatocellular carcinoma; Radiofrequency ablation; Interferon; Secondary prevention

INTRODUCTION

In Japan, the overwhelming majority of hepatocellular carcinoma (HCC) is caused by chronic hepatitis and liver cirrhosis due to persistent hepatitis C or B, mostly hepatitis C virus (HCV) infection. The onset of HCC can be roughly divided into intrahepatic metastasis and multicentric carcinogenesis. The latter can be further divided into synchronous multicentric carcinogenesis, in which HCC occurs in multiple locations simultaneously, and asynchronous multicentric carcinogenesis, in which HCC occurs some time after localized therapy such as partial hepatectomy, percutaneous ethanol injection therapy (PEIT), or percutaneous radiofrequency ablation (RFA). With asynchronous multicentric carcinogenesis, the prognosis of patients can be improved by preventing carcinogenesis in the remaining liver. HCC is treated by analyzing multiple factors, including: (1) decreased hepatic function due to chronic hepatitis and cirrhosis; (2) multicentric carcinogenesis (synchronous/asynchronous) due to persistent infection; and (3) early intrahepatic metastasis due to portal invasion, which is one of the characteristics of HCC. In other words, unlike other cancers, it is necessary to assess not only cancer progression, but also the hepatic reserve. The main objective of interferon (IFN) therapy for chronic hepatitis C infection is to end persistent infection and prevent the progression of liver disease. The present article discusses the significance of IFN therapy as secondary prevention after localized therapy for HCC, particularly IFN therapy combining pegylated IFN (PEG-IFN) and ribavirin.

Table 1 Univariate and multivariate analyses on the carcinogenic factors for HCC in patients with HCV cirrhosis

Variables	Number of patients	Univariate analysis			Multivariate analysis		
		P-value[1]	RR[2]	95% CI	*P*-value[3]	RR[2]	95% CI
Sex							
Male	85	$P = 0.001$	1.971	1.298-2.991	$P = 0.005$	2.107	1.198-2.987
Female	80		1			1	
Alcohol							
Yes	49	$P = 0.012$	1.681	1.108-2.550	NS ($P = 0.496$)	1.234	0.673-2.262
No	116		1			1	
ALT							
⩾ 100	77	$P = 0.013$	1.657	1.103-2.489	NS ($P = 0.876$)	1.050	0.572-1.927
< 100	88		1			1	
LDH							
⩾ 480	74	NS ($P = 0.064$)	-	-	NS ($P = 0.112$)	0.673	0.413-1.096
< 480	91					1	
HCV-RNA							
⩾ 1.0 Meq/mL	110	$P = 0.018$	1.709	1.086-2.695	$P = 0.028$	1.658	1.125-2.315
< 1.0 Meq/mL	55		1			1	
Ant i-HBc							
Positive	78	NS ($P = 0.834$)	-	-	NS ($P = 0.577$)	1.136	0.724-1.782
Negative	87					1	

[1]*P*-values were obtained by using the log-rank test; [2]RR were calculated by comparing classes with Cox regression analysis; [3]*P*-values were obtained by using Cox regression analysis. RR: Relative risks; CI: Confidence interval; NS: Not significant.

ABLATION THERAPY FOR HCC

Unlike other cancers, the treatment of HCC involves not only the stage of the carcinoma itself, but also the stage of underlying chronic hepatitis. In patients with advanced HCC or extrahepatic metastasis, chemotherapy is mostly performed and its usefulness has been shown[1-5]. However, in patients with stage I or Ⅱ HCC, including early-stage HCC, percutaneous therapy is useful because its impact on normal hepatocytes is relatively small. Percutaneous therapy began with PEIT[6] and advanced to percutaneous microwave coagulation therapy (PMCT)[7], and today, RFA that combines the advantages associated with the previous two techniques is often performed[8-10]. In Japan, RFA was first performed in 1999, and it is still premature to discuss its long-term results, but regarding overseas results, Rossi *et al*[8-10] have reported that the survival rate for RFA was 94% at 1 year, 68% at 3 years, and 40% at 5 years, and that the rate of local recurrence was 5% with an average follow-up of 22.6 mo. At present, three RFA needles are available: Radionics Cooltip (single needle), RTC LeVeen probe (expandable needle), and RITA Model 90/70 (expandable needle). In our department, different RFA needles are used depending on tumor site and size, and according to our data, the extent of thermocoagulation per single ablation for RITA Model 90 is 43.2 mL, which is significantly greater when compared to the others. The rate of local recurrence within a range of 20 mm or 30 mm is significantly lower for RITA Model 90 (data not shown). Ablation therapy appears useful for the local control of HCC, but even if local control is sufficient, it is necessary to take into account background liver factors when suppressing recurrence. In other words, as in chronic hepatitis B [11], it is important to treat chronic hepatitis C using IFN.

CARCINOGENIC FACTORS IN HCV-RELATED CHRONIC HEPATITIS

While the onset mechanism of HCV HCC has not been elucidated, it has been suggested that persistent HCV-induced inflammation causes abnormally high levels of transaminase and results in excessive cellular turnover consisting of hepatocyte necrosis and regeneration, thus increasing the risk for genetic abnormalities leading to carcinogenesis. We examined carcinogenic factors in patients with HCV cirrhosis and advanced liver fibrosis; long-term follow-up examinations revealed that high viral titer, sex (male), and age (elderly) were significant onset factors (Tables 1 and 2)[12]. Hence, it is necessary to prevent HCC in patients with these risk factors.

PRIMARY PREVENTION OF HCV-RELATED CHRONIC HEPATITIS BY IFN THERAPY

Many studies have documented that IFN significantly suppresses the onset of HCC from chronic hepatitis and liver cirrhosis. Studies have found that IFN therapy for HCV infection is useful in suppressing carcinogenesis and improving liver function[13,14] and that IFN therapy eliminates HCV RNA and clearly suppresses the onset of HCC in patients with normalized transaminase levels[15]. Additionally, even if a complete response is not achieved, IFN therapy suppresses HCC when compared to untreated cases[16].

Furthermore, even in the presence of advanced chronic hepatitis, cirrhosis improves in about half of patients with a sustained response to IFN therapy[17], and IFN therapy lowers transaminase, maintains platelet counts, and reduces carcinogenesis[13]. This suggests

Table 2 Univariate and multivariate analyses of the carcinogenic factors for HCC in male patients with HCV cirrhosis

Variables	Number of patients	Univariate analysis			Multivariate analysis		
		P-value[1]	RR[2]	95% CI	*P*-value[3]	RR[2]	95% CI
Age (yr)							
⩾ 60	43	*P* = 0.032	1.726	1.032-2.881	*P* = 0.035	4.469	1.271-5.723
< 60	42		1			1	
Alcohol							
Yes	45	*P* = 0.826	1.058	0.632-1.771	NS (*P* = 0.676)	0.877	0.473-1.025
No	40		1			1	
Smoking							
Yes	36	*P* = 0.566	0.863	0.517-1.440	NS (*P* = 0.696)	0.893	0.504-1.580
No	49		1			1	
AST							
⩾ 100	47	*P* = 0.213	1.376	0.824-2.298	NS (*P* = 0.151)	1.863	0.797-4.350
< 100	38		1			1	
ALT							
⩾ 100	46	*P* = 0.805	1.064	0.643-1.763	NS (*P* = 0.485)	0.752	0.337-1.667
< 100	39		1			1	
γ-GTP							
⩾ 80	41	*P* = 0.509	1.182	0.714-1.954	NS (*P* = 0.561)	1.178	0.679-2.041
< 80	44		1			1	
Anti-HBc							
Positive	43	*P* = 0.111	1.522	0.898-2.577	NS (*P* = 0.099)	1.609	0.914-2.835
Negative	42		1			1	

[1]*P*-values were obtained by using the log-rank test; [2]RR were calculated by comparing classes with Cox regression analysis; [3]*P*-values were obtained by using Cox regression analysis. RR: Relative risks; CI: Confidence interval; NS: Not significant.

Table 3 Studies in which IFN was administered after treatments for HCV-related HCC in Japan

Authors	Treated *vs* untreated	Treatment	Follow-up (mo)	Recurrence (%)	Survival (%)
Ikeda[21]	20 *vs* 10	IFN-β	25	10 *vs* 70 ($P = 0.0004$)	
Kubo[22]	15 *vs* 15	IFN-α	36	33 *vs* 80 ($P = 0.037$)	
Suou[23]	18 *vs* 28	IFN-α	60	28 *vs* 82 ($P < 0.01$)	0 *vs* 27 ($P < 0.05$)
Shiratori[24]	49 *vs* 25	IFN-α	84	80 *vs* 92[1]	53 *vs* 23

[1]IFN therapy did not markedly lower the rate of recurrence the first time, it significantly lowered the rate of recurrence the second and third times.

that IFN suppresses persistent hepatitis in liver cirrhosis and carcinogenesis. Regarding the onset of HCC, it is not clear if it is important to maintain low transaminase levels or suppress liver fibrosis, but it is highly likely that blocking fibrosis is important in suppressing carcinogenesis. Therefore, IFN therapy appears to prevent liver fibrosis in liver cirrhosis.

Ever since the national health insurance system began covering IFN therapy in 1992, antiviral therapy for hepatitis C has steadily advanced and at present, therapy combining PEG-IFN and ribavirin is considered the most potent. The combination therapy was markedly effective in about 90% of patients with genotype-2 HCV when administered for 24 wk[18], and it was markedly effective in about 50% of patients with intractable hepatitis (genotype-1 HCV or high viral load) when administered for 48 wk[19]. In Japan, PEG-IFN and ribavirin combination therapy has improved the therapeutic results for intractable chronic hepatitis C.

IFN THERAPY AS SECONDARY PREVENTION FOR RECURRENT HCC

IFN therapy has been performed to prevent recurrent HCC (Table 3). One study retrospectively investigated recurrence after curative resection of HCV HCC, and found that alanine aminotransferase levels remained high[20]. In other words, hepatocyte necrosis and inflammation appear to be closely involved with recurrence. If IFN is successful in lowering HCV to an undetectable level, necrotic inflammation is naturally improved. At the same time, carcinogenesis is believed to be suppressed even in biochemical responders. Ikeda *et al*[21] have investigated the suppression of recurrent HCC by IFN-β following surgical resection or PEIT for HCC in patients with HCV cirrhosis. They have reported that intermittent IFN-β administration following surgical resection or PEIT for HCV HCC suppresses recurrence.

Kubo *et al*[22] have conducted a randomized controlled trial of postoperative IFN therapy in patients with HCV HCC and have reported that the rate of recurrence is significantly lower for patients with IFN therapy.

Suou *et al*[23] administered 6 MU of IFN-α for 24 wk and reported that the 3-year survival rate for patients without IFN-α was 18% and that of patients with IFN-α was 63%. Additionally, Shiratori *et al*[24] have reported that while IFN therapy does not markedly lower the rate of recurrence the first time, it significantly lowers the rate for the second and third times. Hence, IFN may initially act on tumors to suppress intrahepatic micrometastases following therapy for HCC, and then it may act on the virus to suppress recurrence 3-5 years later. Furthermore, it is reported to the contrary that although the cumulative recurrence rate in the IFN group was found to be lower than in the control group during the first 3 years after commencement of IFN administration, the recurrence rate in the IFN group increased with the lapse of time over 3 years. However, long-term, low-dose, intermittent IFN therapy successfully delayed clinical recurrence of HCC after radical RFA therapy[25]. In these studies, IFN therapy consisted of non-PEG-IFN monotherapy and the rate of sustained viral response was low, at 13%-33%. Therefore, if PEG-IFN and ribavirin combination therapy further improves antiviral effects[26], then recurrence may be suppressed even more. However, many patients with HCV HCC are elderly or have cirrhosis, and the dose and duration of PEG-IFN and ribavirin combination therapy have not been established in these patients. Further investigations are warranted.

IFN therapy following therapy for HCC is safe in selected patients. However, IFN therapy for the prevention of recurrent HCC is different from that for the treatment of primary HCC. Because prevention involves not only inflammation, fibrosis, and HCV, but also HCC-related factors, further investigations, including randomized controlled trials, are needed. Furthermore, antiviral therapy itself may improve liver reserve and expand the therapeutic options at the time of recurrence, thus improving the prognosis of HCC, and this issue also needs to be addressed by further studies including randomized controlled trials.

CONCLUSION

Secondary prevention of HCC is an important clinical issue because the recurrence rates of HCC are extremely high even after effective local treatment with hepatic resection or percutaneous ablation. This involves multicentric carcinogenesis in which new lesions are formed as a result of underlying hepatitis. Therefore, IFN therapy following the treatment for HCC is safe in selected patients and IFN therapy is an effective secondary prevention. In the future, PEG-IFN and ribavirin combination therapy may prove to be effective in preventing recurrence, and further investigations involving more cases are needed.

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