Antiviral Therapy in Patients after Treatment for Hepatitis C-Related Hepatocellular Carcinoma

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Background/Aims: Despite great progress, antiviral treatment for chronic hepatitis C in patients with prior hepatocellular carcinoma (HCC) has been rarely investigated. We evaluated the efficacy and safety of antiviral therapy following treatment for hepatitis C-related HCC. **Methods:** Thirteen patients (age 34 to 60 years) who were treated with peginterferon plus ribavirin after treatment for HCC were reviewed. **Results:** There were 6 patients with genotype 1 and 7 patients with genotype 2. All patients showed advanced fibrosis ($\geq F3$) but belonged to the Child-Pugh class A. Treatment was stopped in 2 patients because of recurrent HCC and in 1 patient due to a lack of early virologic response. Seven patients achieved sustained virologic response and three patients relapsed. The sustained virologic response rate was 54% overall, 17% in genotype 1, and 86% in genotype 2. No significant adverse events were reported. **Conclusions:** Antiviral therapy should not be excluded in patients who were previously treated with HCC with genotype 2 chronic hepatitis C, in which an efficacious antiviral treatment for chronic hepatitis C was feasible. Additional study is needed to prove the validity of antiviral therapy in patients with genotype 1 hepatitis C-related HCC. (*Gut Liver* 2011;5:77-81)

Key Words: Chronic hepatitis C; Hepatocellular carcinoma; Peginterferon; Ribavirin

INTRODUCTION

Cirrhosis or hepatocellular carcinoma (HCC) develops in about a third of chronic hepatitis C (CHC) patients over a period of 20 years.¹ However, it is well known that disease progression can be halted by achievement of a sustained virologic response (SVR)

following antiviral therapy.²⁻⁴ Although treatment outcomes have evolved greatly since combination therapy was introduced to treat CHC,⁵⁻⁷ antiviral treatment in patients with CHC-related HCC has rarely been reported.

This study was aimed to evaluate the efficacy and safety of antiviral therapy in CHC patients after treatment for HCC.

MATERIALS AND METHODS

1. Patients

The medical records of 283 patients who received combination therapy with peginterferon (pegIFN) and ribavirin from May 2002 to July 2008 were reviewed. Among them, patients having prior appropriate treatment for HCC and no evidence of viable HCC at the start of antiviral therapy were enrolled. Patients with other liver disease such as chronic hepatitis B, a history of alcohol ingestion (≥ 30 g/day), human immunodeficiency virus infection, or obesity (body mass index ≥ 27 kg/m²) were excluded. After or during antiviral treatment, alpha-fetoprotein combined with imaging study of a dynamic computed tomography or abdominal ultrasonography was checked every 3 months.

One hundred eighty μ g of pegIFN α -2a (Pegasys[®]; Hoffmann-La Roche, Basel, Switzerland) once a week was injected subcutaneously. Ribavirin (Viramid[®]; Ilsung Pharmaceuticals Co., Seoul, Korea) was given orally twice daily at a dose of 1,000 mg/day for patients weighing 75 kg or less and 1,200 mg/day for those weighing more than 75 kg for genotype 1; 800 mg/day was given for genotypes 2 and 3. Duration of treatment was 48 weeks for genotype 1 and 24 weeks for genotype 2, 3. Three hundreds μ g of granulocyte-colony stimulating factor (G-CSF, Leucostim[®]; Dong-A Pharmaceuticals, Seoul, Korea) or 2,000 IU

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of human recombinant erythropoietin (rEPO; Eprex[®]; Janssen Korea, Seoul, Korea) was given twice a week subcutaneously when absolute neutrophil count decreased to less than 500/mm³ or hemoglobin level decreased to less than 8.0 g/dL, by the physician's discretion.

2. Laboratory evaluation

All patients were positive for the anti-hepatitis C virus (HCV) antibody (ADVIA centaur[®] XP assay; Bayer Healthcare LLC, Diagnostics Division, Tarrytown, NY, USA) test using serum. Qualitative HCV RNA was detected by an RNA PCR and hybrid method (COBAS[®] AmpliCor HCV test version 2.0; Roche Molecular Systems, Branchburg, NJ, USA; detection limit, 50 IU/mL), and the serum concentration of HCV RNA was evaluated by RT-PCR (COBAS[®] AmpliPrep/COBAS[®] TaqMan[®] HCV Test; Roche Molecular Systems). Genotyping of HCV was performed in serum obtained for quantitation. Based on the reverse hybridization principle, nested polymerase chain reaction (PCR) was performed with biotinylated primers from the 5' untranslated region, and the second-round product was genotyped with a second-generation line probe assay (INNO-LiPA HCV II; Innogenetics, Ghent, Belgium).

3. Definition

Clinical diagnosis of liver cirrhosis was based on a platelet level less than 100,000/mm³ with radiologic evidence of cirrhotic features or evidence of complications resulting from portal hypertension such as ascites or esophageal varix.

Early virologic response (EVR) was defined as a ≥ 2 log₁₀ reduction of serum HCV RNA after 12 weeks of therapy. End of

treatment response (ETR) was defined as undetectable HCV RNA at the end point of treatment. SVR was defined as undetectable HCV RNA 24 weeks after completion of antiviral therapy maintained throughout the remaining documented follow-up period.

An adherence to antiviral therapy was defined as the actual dose administered divided by the total dose first expected.

4. Statistical analysis

All data are expressed as mean $\pm$ standard deviation with ranges in continuous variables and numbers with percentage in categorized variables, unless otherwise indicated. Binary logistic regression analysis was used to estimate adjusted odds ratios for achievement of IVR. Those analyses were performed using SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA). p-values less than 0.05 were considered to be statistically significant.

RESULTS

There were 12 male and one female patients and mean age of patients was 58 $\pm$ 9.4 years. The number of tumors was 3 or less than in all patients. TNM stage by modified Union Internationale Contre le Cancer (UICC) classification⁸ was I in 9 patients and II in 4 patients. For treatment, transarterial chemoembolization (TACE), radiofrequency ablation or surgery was performed. Mean ALT level at initiation of antiviral treatment was 133 $\pm$ 52 U/L. Advanced fibrosis of F3 or F4 by histology or clinical cirrhosis was confirmed in all of 13 patients. Before antiviral therapy, liver function of all patients belonged to Child-Pugh class A (Table 1).

Mean time from the treatment for HCC to start of antiviral

Table 1. Characteristics of Patients Who Received Antiviral Therapy against Chronic Hepatitis C after Hepatocellular Carcinoma Treatment

Case	Sex	Age, yr	BMI, kg/m ²	WBC, /mm ³	Hb, g/dL	PLT, $\times 10^3$ /mm ³	ALT, U/L	PT, INR	Albumin, mg/dL	TB, mg/dL	Ascites	Encephalopathy	C-P score	Measurement of fibrosis
1	M	59	23.8	2,380	13.4	55	195	1.20	3.1	0.8	Absent	Absent	6	CT: cirrhotic liver
2	M	53	23.5	4,890	14.2	89	155	1.17	3.4	0.5	Absent	Absent	6	Histology: bridging fibrosis
3	F	56	23.1	3,700	12.5	92	190	1.11	3.2	1.1	Absent	Absent	6	CT: cirrhotic liver
4	M	65	16.4	4,420	13.7	119	59	0.98	4.0	0.8	Absent	Absent	5	Histology: bridging fibrosis
5	M	52	26.7	4,380	15.2	40	157	1.19	3.8	0.5	Absent	Absent	5	Histology: cirrhosis
6	M	66	23.4	6,980	13.4	114	140	1.09	4.3	0.7	Absent	Absent	5	Histology: cirrhosis
7	M	67	25.9	4,940	14.2	71	90	1.12	3.6	0.7	Absent	Absent	5	CT: cirrhotic liver
8	M	68	20.5	3,470	13.2	95	208	1.18	3.6	0.5	Absent	Absent	5	Histology: cirrhosis
9	M	60	22.8	4,980	11.2	153	165	1.06	3.5	1.0	Absent	Absent	6	Histology: bridging fibrosis
10	M	62	30.4	2,710	14.8	92	109	1.18	3.3	0.8	Absent	Absent	6	CT: cirrhotic liver
11	M	49	20.6	3,020	18.3	146	135	1.15	3.8	0.7	Absent	Absent	5	Histology: bridging fibrosis
12	M	34	29.0	7,530	15.9	161	51	1.03	4.1	0.7	Absent	Absent	5	CT: cirrhotic liver Endoscopy: varices
13	M	63	26.1	4,520	14.7	73	78	1.25	4.1	0.8	Absent	Absent	5	Histology: cirrhosis

BMI, body mass index; HCV, hepatitis C virus; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; PT, prothrombin time; TB, total bilirubin; C-P score, Child-Pugh score; CT, computed tomography.

Table 2. Clinical Data Regarding Prior Hepatocellular Carcinoma and Antiviral Treatment against Chronic Hepatitis C

Case	TNM stage	Treatment modality for HCC	Time interval from HCC treatment, wks	Geno-type	HCV RNA, IU/mL	Adherence to pegIFN/ribavirin, %	Adjuvant management	Virologic response	Recurrence, mo	Follow-up duration, mo
1	I	TACE	100	1	2,270,000	100/100	-	Stop due to EVR (-)	1	63
2	I	Surgery	41	1	1,918,080	100/100	-	Relapse	7	49
3	I	RFA	53	1	315,684	78/100	G-CSF	SVR	-	54
4	II	Surgery	57	1	154,845	-	-	Dropout at wk 8 (HCC recurrence)	-	53
5	I	Surgery	35	1	2,387,610	100/91	-	Relapse	-	46
6	I	Surgery	41	1	1,910,000	-	-	Dropout at wk 14 (HCC recurrence)	-	34
7	II	TACE	35	2	54,108	100/82	-	SVR	11	62
8	II	RFA	61	2	529,000	100/100	-	SVR	3	67
9	II	Surgery	13	2	135,600	54/65	G-CSF & rEPO	SVR	-	65
10	I	RFA	62	2	179,000	100/100	-	SVR	4	66
11	I	Surgery	95	2	24,575	100/100	-	SVR	-	54
12	I	RFA	29	2	87,800	100/100	-	Relapse	14	34
13	I	Surgery	163	2	51,100	100/100	-	SVR	-	26

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; pegIFN, peginterferon; TACE, transarterial chemoembolization; EVR, early virologic response; RFA, radiofrequency ablation; G-CSF, granulocyte-colony stimulating factor; SVR, sustained virologic response; HCC, hepatocellular carcinoma.

Fig. 1. Flow chart of this study.

EVR, early virologic response; SVR, sustained virologic response.

therapy was 60 ± 44 weeks. Six patients were genotype 1 and 7 patients were genotype 2. Antiviral therapy was stopped in 2 patients with genotype 1 because of HCC recurrence, thus a total of 11 patients (85%) completed the treatment protocol. Among those followers, 11 patients showed ETR and 8 patients achieved SVR (Table 2, Fig. 1). The SVR rate was 54% (7/13) overall, and 86% (6/7) in the genotype 2 patients (Fig. 2).

Overall adherence of followers to treatment was 93%. The adherence to pegIFN and ribavirin was 93%. Two patients received G-CSF because of a significant reduction of neutrophil count and one patient received rEPO due to anemia. There was no serious adverse event requiring cessation of antiviral therapy.

The median follow-up period following the end of treatment was 54 (26-67) months. After treatment, HCC recurred in 5 patients.

Fig. 2. Response to antiviral therapy according to genotype.

EVR, early virologic response; SVR, sustained virologic response.

DISCUSSION

Although antiviral therapy has far evolved, patients with CHC-related HCC are still known for “difficult-to-treat” because they usually have advanced fibrosis.^{6,7,9,10} Major issues in antiviral therapy for those patients are frequent adverse events and the subsequent low adherence to the therapy. Anemia and neutropenia are leading causes for premature discontinuation,¹¹ and those hematologic adverse events frequently develop in the elderly, patients with low baseline cell counts, liver cirrhosis, and low body weight (<60 kg).¹²⁻¹⁴ Considering those predisposing factors, it is no wonder physicians are reluctant to treat CHC in patients who are already diagnosed with HCC.

Recent several studies about CHC-related compensated cirrhosis presented a premature discontinuation rate of 11–33% with pegIFN and ribavirin combination therapy.^{15–17} On the contrary, there was no serious adverse event requiring discontinuation of treatment in our study. Dropout cases were not induced by poor compliance, but HCC recurrence. The mean adherence to both of pegIFN and ribavirin was 93%. Authors attribute good hepatic function (child A) and favorable condition (median body mass index 24 kg/m²) to considerable adherence in this study. In addition, seasoned experience as a tertiary hospital may help for managing adverse event.

In this study, the overall SVR rate was 54%, and increased up to 86% in genotype 2 patients. The results are comparable to prior reports of patients with advanced fibrosis without HCC, where the SVR rate was 43–52% overall and 72–75% in genotype 2, 3 by pegIFN plus ribavirin treatment.^{6,7,10,15} Our data suggest that a favorable outcome can be obtainable for CHC-related HCC patients with genotype 2. Meanwhile, the result was disappointing in genotype 1 in even taking into small number of patients, unexpected recurrences of HCC, and higher RNA level than genotype 2. Recent study regarding similar issue has reported that lower SVR rate in genotype 1 patients compared with cirrhotic patients were caused by poor compliance.¹⁸ The evidence to support antiviral therapy in genotype 1 CHC after HCC yet lacked.

Whether antiviral treatment for patients with established HCC can prevent further progression is an important matter. IFN has been proven to have a preventive effect against HCC by anti-proliferative action *in vivo* and *vitro*.^{19–22} Several studies have demonstrated that disease course was improved by IFN-based treatment even without SVR.^{2,23–25} These beneficial effects of IFN are attested by reduction in recurrence of HCC,^{26–29} especially late recurrences (after 2 years).^{27,29} However, HCC recurred in 5 patients within 1 year in this study. Our interpretation of these opposite results is that high recurrence rate in this study may be associated with the modality of treatment, because both 2 patients who received TACE experienced recurrences whereas only one of 6 patients who received surgery had recurrence.

This observational report is limited because of small sample size, short duration of follow-up and non-comparative design. Even with achievement of SVR, the recurrence rate of HCC is still high. Nevertheless, we demonstrated good adherence, few adverse events, and satisfactory treatment outcome in CHC-related HCC patients with genotype 2. Therefore, genotype 2 CHC patients who were treated for HCC appropriately should not be deprived of antiviral therapy. Future studies are required to determine the optimal timing to start antiviral therapy and evaluate the effect of subsequent SVR on disease progression and long-term survival, as well as the validity of antiviral therapy in genotype 1 patients.

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