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Short Communication
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Direct-Acting Antiviral Therapy for Treating Patients with Hepatitis C Virus Infection has Anticarcinogenic Effects Similar to Those of Interferon Therapy

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Introduction

The treatment of hepatitis C virus (HCV) infection has advanced rapidly from monotherapy with interferon (IFN) to therapies combining IFN with ribavirin (RBV) or direct-acting antiviral (DAA) agents and even to all oral DAA therapy. DAA therapy has milder side effects than IFN therapy, and a high rate of sustained virological response (SVR) at 12-24 weeks [1,2]. The objective of this study was to investigate whether differences exist in the development of hepatocellular carcinoma (HCC) between IFN-based therapy and DAA therapy.

Materials and Methods

This retrospective study was approved by the Ethics Committee of Dokkyo Medical University Koshigaya Hospital (No. 1602), and conformed to the ethical guidelines of the 2008 Declaration of Helsinki.

Of the 333 patients with HCV infection (hereinafter, HCV patients) enrolled in this study, 179 received IFN-based therapy (IFN group). Patients received the following IFN-based therapies: pegylated interferon (peg-IFN) therapy (22 patients), peg-IFN with RBV (peg-IFN/RBV) therapy (109 patients), and peg-IFN/RBV with DAA agents (peg-IFN/RBV/DAA) therapy (48 patients). The DAA group included 154 patients, all treated with daclatasvir and asunaprevir. Patients with a history of HCC were excluded from this study. Patients who developed HCC within 6 months of completing treatment were also excluded.

All patients were screened using B-mode ultrasonography (US) within 3 months prior to commencing treatment and confirmed that no signs of HCC were present. Contrast-enhanced computed tomography (CT) or gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) magnetic resonance imaging (MRI) was used to eliminate the possibility of HCC comorbidity when a nodule was identified from US.

US were conducted every 3-6 months after treatment completion. Contrast-enhanced CT or Gd-EOB-DTPA MRI was conducted when a nodule was observed on US.

Cox proportional hazard modeling was used to determine whether the type of treatment was associated with the development of HCC.

The following clinical parameters were used as factors associated with the development of HCC: age at the start of treatment; sex; platelet count; Fibrosis-4 (Fib4) index, post-treatment alanine aminotransferase (ALT); and alpha-fetoprotein (AFP).

Statistical Analysis

The age difference between the IFN group and DAA group was adjusted using propensity score matching. Continuous data for clinical parameters are expressed as mean ± standard deviation (SD). The Mann-Whitney U test and chi-squared test were used in comparisons between two groups. The Kaplan-Meier method was used in calculating the cumulative non-carcinogenic curve. A logistic regression model was used in multivariate analysis. The Cox proportional hazard model was used to

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Table 1: Patient background.

	IFN group (n=100)	DAA group (n=100)	p
Age (years)	55.9 ± 11.9 (28-76)	58.0 ± 10.2 (35-74)	0.325
Sex (male/female)	49/51	44/56	0.322
HCV RNA (logIU/ml)	6.0 ± 1.1 (1.8-7.6)	5.9 ± 1.0 (3.4-7.5)	0.466
ALT (IU/L)	68.9 ± 49.4 (12-269)	58.1 ± 42.7 (11-252)	0.108
T-Bil (mg/dl)	0.88 ± 0.44 (0.4-4.24)	0.81 ± 0.42 (0.2-3.17)	0.060
Alb (g/dl)	4.2 ± 0.4 (3.1-5.1)	4.3 ± 0.4 (2.6-5.2)	0.474
WBC ($\times 10^2/\mu l$)	4976 ± 1559 (2000-9400)	5313 ± 1715 (1000-9800)	0.102
Hb (g/dl)	14.2 ± 1.5 (10.0-19.1)	14.1 ± 1.4 (10.5-18.1)	0.902
Plt ($\times 10^4/\mu l$)	15.5 ± 5.6 (4.4-29.9)	15.7 ± 6.1 (4.5-34.0)	0.807
PT (%)	108.8 ± 14.2 (73-139)	103.8 ± 17.6 (34-147)	0.084
AFP (ng/ml)	6.5 ± 16.0 (0.9-16.0)	5.0 ± 4.6 (1.2-27.9)	0.162
Fib4 index	3.22 ± 2.15 (0.40-11.19)	3.41 ± 2.55 (0.74-17.19)	0.851
SVR24 (yes/no)	74/26(74.0%)	97/3 (97.0%)	0.000
Observation period (months)	35.6 ± 21.4 (6-98)	9.9 ± 4.9 (6-20)	0.000
Development of HCC (yes/no)	3/97	3/97	1.000

Table 2: Factors associated with development of HCC (univariate analysis).

	Relative risk	95% Confidence interval	p
Sex (Male)	1.15964	0.23379-5.75197	0.85616
Age (≥ 65 years)	2.31301	0.41960-12.7504	0.33564
Post-treatment ALT (≥ 40 U/L)	0.25741	0.05184-1.27808	0.09694
Platelet count (<15 × $10^4/\mu l$)	4.69598	0.54698-40.3163	0.15855
Fib4 index (≥ 3.25)	3.48373	0.63718-19.0468	0.14987
Post-treatment AFP level (≥ 6 ng/ml)	14.64930	1.70781-125.660	0.01436
SVR 24 (achieved)	1.31597	0.22704-7.62764	0.75941
Type of treatment (DAA)	5.90471	0.61223-56.9482	0.12462

determine factors associated with the development of HCC. Values of $p<0.05$ were regarded as statistically significant.

Results

Mean age was 57.6 ± 10.1 years for the IFN group (n=179) and 67.5 ± 9.5 years for the DAA group, showing a significant difference. After propensity score matching for age, the IFN and DAA groups each included 100 patients. Table 1 shows patient backgrounds. No significant differences were found for sex, blood biochemistry, AFP, or Fib4 index. SVR at 24 weeks post-treatment was significantly higher in the DAA group, at 97.0% compared to the IFN group at 74.0%. The period of observation was significantly longer in the IFN group (35.6 months) than in the DAA group (9.9 months). HCC was found in three patients in the IFN group and three patients in the DAA group.

Table 2 shows the results of analysis using Cox proportional hazard modeling. In terms of factors associated with development of HCC, post-treatment AFP level ≥ 6 ng/ml was identified as the only significant factor. Although the relative risk of developing HCC tended to be higher in the DAA group than in the IFN group, no significant difference was present.

Discussion

Traditional IFN therapy has been shown to have anti-hepatocarcinogenic effects. The incidence of HCC was significantly lower in patients who achieved SVR than in patients who had not achieved SVR [3,4]. On the other hand, some reports have described patients developing HCC many years after achieving SVR, highlighting the importance of screening depending on the risk of developing HCC [5]. DAA agents achieved significantly higher rates of SVR compared with IFN therapy. No consensus has been reached regarding the anticarcinogenic effects of DAA agents. While DAA agents have been shown to demonstrate anticarcinogenic effects similar to those of INF therapy [6], some reports have described DAA therapy as promoting the recurrence of HCC following cure [7,8].

We investigated HCV patients who developed HCC following treatment with IFN and DAA therapies to examine whether the type of treatment was associated with development of HCC. As age greatly affects the development of HCC induced by HCV, propensity score matching was used to match age between groups. This allowed comparison of the two therapy groups without differences in parameters of liver fibrogenesis such as platelet count or Fib4 index.

High AFP levels were found the only factor independently associated with the development of HCC, and no significant difference was detected in the type of treatment (INF or DAA groups) as a factor associated with development of HCC. The result suggests that the anticarcinogenic effects of DAA therapy are similar to those of IFN therapy. On the other hand, the number of patients developing HCC is likely to show an upward trend in the future clinical setting, as DAA therapy is largely performed on elderly patients. Even with

the achievement of SVR following DAA therapy, careful observation is required in patients with an AFP level ≥ 6 ng/ml as they represent a group at high risk of developing HCC.

References

1. Kumada H, Chayama K, Rodrigues L Jr, Suzuki F, Ikeda K, Toyoda H, et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. Hepatology (Baltimore, Md). 2015;62(4):1037-46.
2. Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet (London, England). 2014;384(9954):1597-605.
3. Kurokawa M, Hiramatsu N, Oze T, Mochizuki K, Yakushijin T, Kurashige N, et al. Effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with chronic hepatitis. Hepatol Res. 2009;39(5):432-8.
4. Murphy D, Detjen KM, Welzel M, Wiedenmann B, Rosewicz S. Interferon-alpha delays S-phase progression in human hepatocellular carcinoma cells via inhibition of specific cyclin-dependent kinases. Hepatology (Baltimore, Md). 2001;33(2):346-56.
5. Mashitani T, Yoshiji H, Yamazaki M, Ikenaka Y, Noguchi R, Ishikawa M, et al. Development of hepatocellular carcinoma in a patient 13 years after sustained virological response to interferon against chronic hepatitis C: a case report. Cases Journal. 2009;2(1):18.
6. Kobayashi M, Suzuki F, Fujiyama S, Kawamura Y, Sezaki H, Hosaka T, et al. Sustained virologic response by direct antiviral agents reduces the incidence of hepatocellular carcinoma in patients with HCV infection. J Med Virol. 2016;89(3):476-83.
7. Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016;65(4):719-26.
8. Minami T, Tateishi R, Nakagomi R, Fujiwara N, Sato M, Enooku K, et al. The impact of direct-acting antivirals on early tumor recurrence after radiofrequency ablation in hepatitis C-related hepatocellular carcinoma. J Hepatology. 2016;65(6):1272-3.