Interval between hepatocellular carcinoma treatment and interferon-free direct-acting antiviral agents against hepatitis C is necessary to suppress tumor recurrence

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Abstract. Interferon (IFN) has been identified to suppress carcinogenesis when used for treating hepatitis C virus (HCV) infections. Treatment with IFN-free direct-acting antiviral agents (DAAs) is an acceptable alternative, even in elderly patients or patients who have been treated for hepatocellular carcinoma (HCC), because it has a lower incidence of side effects and higher sustained virological response (SVR) rate compared with IFN treatment. However, the suppression of carcinogenesis by DAAs is unclear. In the present study, 19 patients who underwent DAA treatment following treatment for HCC between January 2015 and March 2017 were retrospectively investigated. The clinical data were compared between 9 patients with HCC recurrence following DAA treatment (recurrence group) and 10 patients without HCC recurrence (no-recurrence group). The 1-year cumulative recurrence rate of HCC following SVR was as high as 50.2%. Age and sex did not significantly differ between the two groups, and the average number of HCC treatments prior to DAA treatment was also not significantly different between the recurrence and no-recurrence groups (3.2 and 2.2, respectively). The median interval between the final HCC treatment and the commencement of DAA treatment was 88 days in the recurrence group, which was significantly less compared with 790 days in the no-recurrence group (P=0.018). An interval of 120 days or more from final HCC treatment to the commencement of DAA treatment was a significant independent factor of no HCC recurrence following DAA treatment (P=0.028). A high HCC recurrence rate was identified following DAA treatment in patients with a history of HCC treatment. Therefore, there should be at least a 4-month interval from the final HCC treatment to the commencement of DAA treatment to ensure no HCC recurrence.

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Abbreviations: AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; HCC, hepatocellular carcinoma; IFN, interferon; DAA, direct-acting antiviral agent; HCV, hepatitis C virus

Key words: hepatocellular carcinoma, interferon-free direct-acting antiviral agents, hepatitis C, tumor recurrence, sustained virological response

Introduction

HCV infection is one of the principal causes of chronic liver disease, with ~170 million individuals infected worldwide (1). The 5-year incidence of HCC from HCV patients is reported to be 13.4%, with a mortality rate of 15.3% (2). Therefore, suppression of HCV is critical, and HCV treatments have been continually developed and improved.

Previously, IFN was the mainstream treatment for HCV. The SVR rate for two drugs (e.g. peginterferon and ribavirin) against HCV genotype 1, which is considered to cause the highest incidence of HCC (3), is ~50%, whereas the use of three drugs (e.g. peginterferon, ribavirin and protease inhibitor) increases the SVR rate to ~70% (1). The SVR from IFN treatment has been identified to decrease the incidence of HCC (3-5). Compared with patients without SVR, the incidence of HCC following SVR from IFN treatment is reportedly decreased by 19.1% (6). In addition, randomized control trials have revealed that the SVR from IFN treatment in patients following HCC treatment decreases tumor recurrence (7,8). Recurrence within 2 years is particularly decreased following HCC treatment (9), as is the rate of liver disease-associated mortality (10,11). However, one study demonstrated that SVR from IFN treatment did not decrease the incidence of HCC in patients with cirrhosis because of background fibrosis (10).

Conversely, it is unclear whether non-SVR following IFN treatment decreases the incidence of HCC. One study demonstrated that non-SVR following IFN treatment decreases the incidence of HCC (12), whereas another indicated no decrease in HCC incidence from non-SVR (6).

Currently, direct-acting antiviral agents (DAAs) are used worldwide as an alternative to interferon (IFN) for the

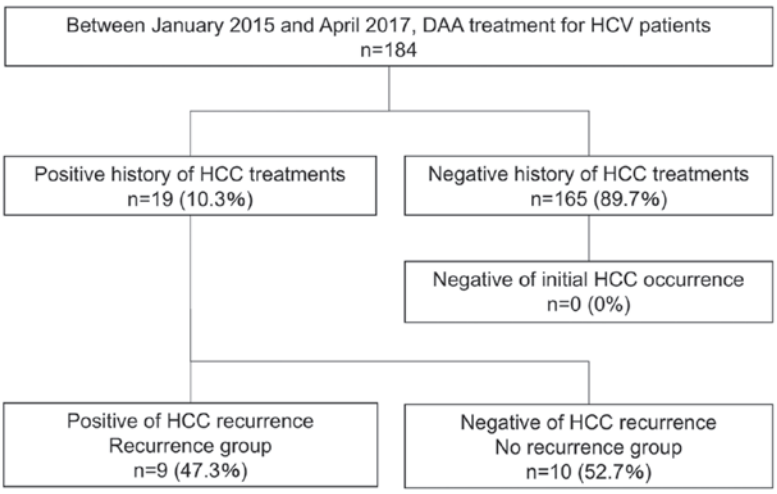

Figure 1. Decision tree of patients undergoing DAA treatment in the present study. DAA, direct-acting antiviral agent; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

treatment of hepatitis C virus (HCV) infections. DAA treatment has a higher sustained virological response (SVR) rate and fewer side effects compared with IFN treatment, so it is acceptable for many elderly patients with HCV infections (13-16). However, several studies have indicated that the rate of hepatocellular carcinoma (HCC) recurrence may be increased following DAA treatment in patients with a history of HCC treatment (17-19). Conversely, there have been several studies indicating that DAAs do not raise the recurrence rate, even following HCC treatments, and instead have a suppressive effect on carcinogenesis (20-22). This discrepancy has not yet been resolved.

Therefore, the aim of the present study was to retrospectively investigate patients with a history of HCC treatments to whom DAAs were administered at Shiga University of Medical Science (Otsu, Japan).

Materials and methods

Patient selection and data collection. Between January 2015 and April 2017, 184 patients with HCV were administered DAAs in Shiga University of Medical Science. Among them, 19 had been treated for HCC prior to commencing DAA treatment. Clinical data were compared between the 9 patients in whom recurrence of HCC was observed following SVR of DAA treatment (recurrence group), and the 10 patients for whom no HCC recurrence was observed following SVR of DAA treatment (no-recurrence group).

Statistical analysis. χ^2 tests were performed for nominal variables, and the Mann-Whitney U test was performed to compare continuous variables between the two groups. The Cox proportional hazards model was used for multivariate analysis. The Kaplan-Meier method was used to analyze the cumulative incidence rate, followed by log-rank tests for comparisons between the two groups. $P<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using the R statistical package (version 3.4.4; The R Project for Statistical Computing, Vienna, Austria; www.r-project.org).

Results

The decision tree for patients in the present study is presented in Fig. 1. Between January 2015 and April 2017, 184 patients underwent DAA treatment, and they all achieved SVR. Among them, 165 patients (89.7%) had no history of HCC treatment, and no patients experienced initial HCC occurrence following DAA treatment. In total, 19 patients (10.3%) had a history of HCC treatment, and 9 of them (47.3%) had HCC recurrence following DAA treatment.

The results of univariate analysis between the recurrence and no-recurrence groups are presented in Table I. No significant differences in age, sex, hemoglobin A1c, serotype of HCV, regimen of DAAs or history of IFN treatment were identified. In the laboratory data, no significant differences were observed in α-fetoprotein (AFP), des-γ-carboxyprothrombin (DCP), albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, hemoglobin, platelet count, or prothrombin activity. Among the tumor-associated factors, there were no significant differences in the number of tumors, the maximum tumor diameter, the number of HCC treatments or the final treatment method for HCC prior to DAA treatment. The only difference observed was in the median interval between final HCC treatment and DAA treatment, which was significantly shorter in the recurrence group compared with in the no-recurrence group (88 and 790 days, respectively; P=0.018).

The results of univariate and multivariate analysis to identify risk factors of tumor recurrence following DAA treatment are presented in Table II. Factors of continuous variables were divided into two groups by their median values. In univariate analysis, a significant difference was observed in the interval between the final HCC treatment and DAA treatment (≥120 vs. ≤119 days; P=0.028). Multivariate analysis was performed using tumor markers (AFP and DCP), the number of HCCs, and the interval between the final HCC treatment and the DAA treatment. From this analysis, only the interval between the final HCC treatment and the DAA treatment was identified as an independent risk factor of HCC recurrence following DAA treatment (P=0.045).

Table I. Univariate analysis between the no-recurrence and recurrence groups.

Factor	No-recurrence group (n=10)	Recurrence group (n=9)	P-value
Mean age, years	74±9.4	74±6.5	0.961
Sex (male), n (%)	6 (60.0)	4 (44.4)	0.656
Median AFP, ng/ml (IQR)	5.60 (4.15, 10.55)	10.90 (7.50, 29.50)	0.111
Median DCP, mAU/ml (IQR)	22.50 (19.50, 40.50)	27.00 (25.00, 31.00)	0.54
Median albumin, g/dl (IQR)	3.55 (3.23, 3.97)	3.50 (3.10, 3.60)	0.389
Median AST, IU/l (IQR)	44.50 (32.00, 55.25)	52.00 (40.00, 73.00)	0.653
Median ALT, IU/l (IQR)	31.50 (26.50, 34.50)	45.00 (27.00, 49.00)	0.683
Median bilirubin, mg/dl (IQR)	0.74 (0.60, 0.93)	0.69 (0.53, 0.78)	0.87
Median hemoglobin A1c, g/dl (IQR)	12.00 (11.62, 12.38)	11.60 (11.20, 12.80)	0.87
Median platelet count, $x10^4$ μl (IQR)	12.65 (8.62, 16.52)	11.40 (10.10, 15.60)	0.87
Median prothrombin activity, % (IQR)	86.00 (81.00, 90.00)	90.00 (84.00, 95.00)	0.479
Multiple HCC, n (%)	3 (30.0)	3 (33.3)	>0.999
Maximum tumor size, mm	25.7±10.3	21.6±17.5	0.573
Treatment history of IFN, %	3 (30.0)	3 (33.3)	>0.999
RFA prior to DAA, %	3 (30.0)	4 (44.4)	0.65
Hepatectomy prior to DAA, %	4 (40.0)	1 (11.1)	0.303
TACE prior to DAA, %	3 (30.0)	4 (44.4)	0.65
Median no. of HCC treatments (IQR)	1.50 (1.00, 5.50)	2.00 (1.00, 2.00)	0.898
HCV serotype, n (%)			0.303
1	6 (60.0)	8 (88.9)	
2	4 (40.0)	1 (11.1)	
Regimen of DAA, n (%)			0.371
DCV+ASV	2 (20.0)	4 (44.4)	
SOF+LDV	4 (40.0)	4 (44.4)	
SOF+RBV	4 (40.0)	1 (11.1)	
Median interval between final HCC treatment and DAA, days (IQR)	790 (308, 2075)	88 (20, 120)	0.018

AFP, α-fetoprotein; IQR, interquartile range; DCP, des-γ-carboxyprothrombin; mAU, milli-arbitrary units; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; IFN, interferon; RFA, radiofrequency ablation; DAA, direct-acting antiviral; TACE, transcatheter arterial chemo-embolization; HCV, positive for hepatitis virus C antibody; DCV, daclatasvir; ASV, asunaprevir; SOF, sofosbuvir; LDV, ledipasvir; RBV, ribavirin.

The cumulative recurrence rate of HCC are shown in Fig. 2. The 180-day cumulative recurrence rate in patients with a period ≤119 days between final HCC treatment and DAA treatment was 44.4%, which was significantly higher compared with the rate for patients with a period of ≥120 days (P=0.028).

Discussion

Recently, IFN-free DAA treatment has been developed, and consequently the SVR rate has increased further to 90% or more (13-16). Use of DAAs is currently the mainstream treatment worldwide (18,23), not only because of its high rate of SVR, but also because fewer side effects occur compared with using IFN. Owing to this decrease in the number of side effects, DAA treatment is also widely used following hepatectomy for HCC in elderly patients, whose numbers have been increasing in recent years (24).

However, there have been several reports of DAA treatment increasing the incidence of HCC. Initially, one study identified that 16/58 (27.6%) of patients with HCC following treatment had a median recurrence of 5.7 months (17). Subsequently, several other studies have identified recurrence rates close to 30% following HCC treatment, <6 months after DAA treatment (18,19). These results suggest that DAA treatment may promote carcinogenesis in patients with HCC with a history of treatment. However, it has not yet been determined whether DAA treatment promotes carcinogenesis in patients with no HCC treatment history (1,18,19,25-27).

Several reasons have been proposed for the increase in HCC recurrence by DAA treatment, as described below. It is considered that the mechanism of carcinogenesis following DAA treatment involves changes in IFN gene expression and natural killer cell function (28). IFN has anticancer effects and acts in immunoregulation by prolonging all phases of the cell cycle (28). In contrast, DAA treatment causes downregulation of IFN genes and increases cell proliferation without appropriate regulation by checkpoints. Consistently, it has been reported that serum vascular endothelial growth factor,

Table II. Univariate and multivariate analysis for evaluation of risk factors of HCC recurrence.

		Univariate analysis		Multivariate analysis	
Factor	n	Median survival	P-value	Hazard ratio (95% confidence interval)	P-value
Age, years			0.703		
<75	9	NA (60-NA)			
≥75	10	365 (20-NA)			
Sex			0.783		
Female	9	365 (150-NA)			
Male	10	NA (20-NA)			
AFP, ng/ml			0.783	0.50 (0.11-2.28)	0.37
<9	10	NA (20-NA)			
≥9	9	365 (150-NA)			
DCP, mAU/ml			0.323	0.92 (0.18-4.57)	0.92
<25	9	NA (60-NA)			
≥25	10	329 (20-NA)			
Albumin, mg/dl			0.783		
<3.5	9	365 (150-NA)			
≥3.5	10	NA (20-NA)			
AST, IU/l			0.223		
<50	9	NA (20-NA)			
≥50	10	300 (30-NA)			
ALT, IU/l			0.624		
<35	10	NA (20-NA)			
≥35	9	329 (30-NA)			
Bilirubin, mg/dl			0.267		
<0.7	10	272.5 (20-NA)			
≥0.7	9	NA (150-NA)			
Hemoglobin, g/dl			0.861		
<12	10	365 (150-NA)			
≥12	9	NA (20-NA)			
Platelet count, x10^4 μl			0.592		
<11	9	NA (150-NA)			
>11	10	300 (20-NA)			
Prothrombin activity, %			0.506		
<90	10	NA (20-NA)			
≥90	9	300 (30-NA)			
Number of HCC			0.907	1.92 (0.39-9.40)	0.42
Single	13	329 (160-NA)			
Multiple	6	365 (20-NA)			
Maximum size of HCC, mm			0.108		
<20	11	329 (60-NA)			
>20	8	NA (20-NA)			
History of IFN			0.765		
Absence	13	NA (60-NA)			
Presence	6	365 (160-NA)			
RFA prior to DAA			0.389		
Absence	12	NA (60-NA)			
Presence	7	300 (30-NA)			
Hepatectomy prior to DAA			0.181		
Absence	14	329 (150-NA)			
Presence	5	NA (60-NA)			

Table II. Continued.

		Univariate analysis		Multivariate analysis	
Factor	n	Median survival	P-value	Hazard ratio (95% confidence interval)	P-value
TACE prior to DAA			0.642		
Absence	12	NA (60-NA)			
Presence	7	365 (20-NA)			
Number of HCC treatments			0.38		
1	8	NA (60-NA)			
≥2	11	365 (30-NA)			
Interval between final HCC treatment and DAA, days			0.0284	8.25 (1.05-65.18)	0.045
≤119	9	300 (20-NA)			
≥120	10	NA (30-NA)			

NA, not available; AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; mAU, milli-arbitrary units; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; IFN, interferon; RFA, radiofrequency ablation; DAA, direct-acting antivirals; TACE, transcatheter arterial chemo-embolization.

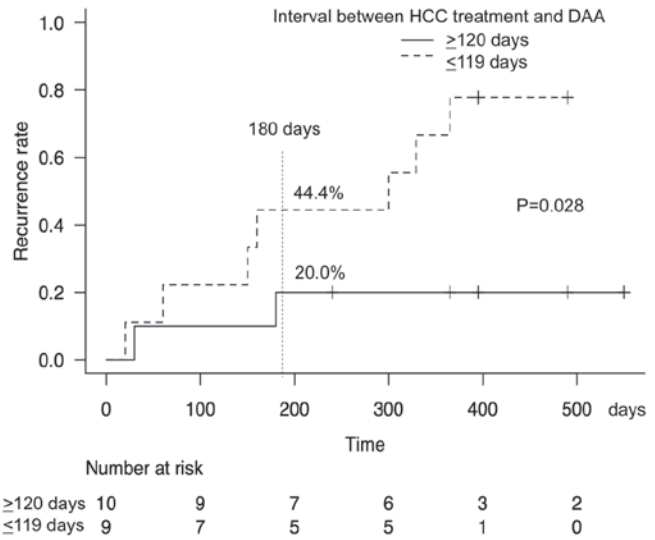

Figure 2. Cumulative recurrence rate of HCC, divided according to the period between the final HCC treatment and DAA treatment (≥120 vs. ≤119 days). The incidence of recurrence for the ≤119-days group was significantly higher compared with that of the ≥120-days group (44.4 vs. 20.0%; P=0.028). HCC, hepatocellular carcinoma; DAA, direct-acting antiviral agent.

angiogenesis and the size of HCC are increased 4 weeks after the administration of DAAs (29). Although these results have led to concern that DAAs cause carcinogenesis, this has not yet been demonstrated, and further research is required. Of relevance, the results of the present study indicated that patients treated for HCC had a high recurrence rate. The statistical analyses indicated that an interval of 4 months after HCC treatment is required to prevent recurrence. This result is similar to that of a study published previously (30). It is not clear why the 4-month interval is required. However, divisions of 4 months were determined statistically using the median value.

Currently, IFN has been reported to be cost-effective because it decreases liver disease-associated mortality (31), but it is more expensive compared with DAAs with borderline treatment benefits (32). If it becomes clear that there are a number of recurrences of HCC following DAA treatment, its cost-effectiveness may be very poor. Therefore, further consideration of the relative value of IFN and DAA treatment is required. We hypothesize that the residual lesion following HCC treatment may be associated with recurrence following DAA treatment.

A decrease in the incidence of HCC following DAA treatment was identified in a large cohort study of ~17,000 patients with HCV (33). However, the incidence of HCC by DAA treatment in patients with a history of HCC was unclear in the conclusion of this paper. It was concluded that DAAs were administered to patients at high risk of developing HCC. In addition, several meta-analyses and review articles have been published. All concluded that DAA treatment decreased the incidence of initial HCC (34-36). However, DAA treatment for HCC recurrence has not yet verified. The findings of these studies highlighted the requirement for high-quality prospective studies, because the studies included heterogeneous cohorts, potential misclassification of HCC absence prior to administration of DAAs, ascertainment bias for recurrence and short durations of follow-up (34-36).

One meta-analysis focused on the interval from treatment of HCC to DAA administration. The results indicated that patients with a 6-month interval between treatment of HCC and DAA administration decreased the recurrence rate of HCC. Between the treatment of liver cancer and administration of DAAs, cases with a period of ~6 months resulted in lowering the recurrence rate of HCC (37). The results of the present study indicated that a 4-month interval was required, but it should be determined whether or not the interval is vital, and, if so, for how long it is required.

The limitations of the present study are that the number of patients was small, and it was a single institutional study. Larger prospective studies with large multicenter cohorts are required.

In conclusion, the recurrence rate following DAA treatment may be high in patients with a history of HCC treatment. To prevent recurrence, an interval of ≥4 months between HCC treatment and the administration of DAAs is advised. However, the results are preliminary, and a larger cohort study or much longer observation period may be required to obtain reliable conclusions.

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Availability of data and materials

The data used in the present study are available from the corresponding author on reasonable request.

Authors' contributions

HI designed the research and analyzed the patient data. HI, RO, TF, HMa, HMo, NK, AA and MT performed the interventions. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study conformed to the Clinical Research Guidelines and was approved by the ethical committee of Shiga University of Medical Science (Otsu, Japan; approval no. 27-233). Informed consent was obtained from all patients or members of their families prior to surgery.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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