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Retrospective Study

Direct-acting antivirals for hepatitis C virus-infected patients with hepatocellular carcinoma

DAA-therapy in HCC patients

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) in hepatitis C virus (HCV) infected patients has a high risk of recurrence. Although eradication of HCV is expected to reduce this risk, it may be high after treatment with direct-acting antivirals (DAA) in patients with a history of HCC.

AIM

Our aim was to clarify the risk factors of HCC recurrence in HCV patients with an HCC history.

METHODS

We retrospectively analyzed the risk of HCC (re)occurrence (a coined term to include recurrence in patients with an HCC history and/or occurrence in those without an HCC history) after DAA-therapy in 311 HCV patients with and without a history of HCC treated at our institution and several neighboring hospitals. Previous known predictors regarding HCC (re)occurrence after DAA-therapy and the frequency of HCC (re)occurrence were included in our analyses. The clinical course of HCC before and after DAA-therapy was also evaluated.

RESULTS

HCV patients with, than without, an HCC history were older and had a greater progression of liver fibrosis and diabetes. Median recurrence-free survival (RFS) was 1,092 days in patients with an HCC history, and post-DAA therapy HCC (re)occurrence was observed in 29 patients (53.7%) with, and 5 patients (1.9%) without, an HCC history during the 6-year study period ($p<0.001$). HCC (re)occurrence was more frequent in patients with, than without, an HCC history. There was no significant difference in RFS among those with an HCC history between pre- and post-DAA-therapy periods. The frequency of HCC (re)occurrence in patients with an HCC history was relatively

decreased during the post-DAA-therapy period. In multivariate analysis, only incidence rate of pre-DAA-therapy HCC (re)occurrence was an independent predictive factor of HCC (re)occurrence after DAA-therapy. In patients with HCC (re)occurrence after DAA-therapy, liver function was well-preserved and the clinical course was good.

CONCLUSION

DAA-therapy in patients with HCV infection is a useful treatment option also in those patients with a history of HCC. Curative treatment for HCC is desirable before DAA-therapy. The frequency of HCC (re)occurrence before DAA-therapy was associated with significantly increased risk of HCC recurrence after DAA-therapy. Careful observation after DAA-therapy is required in patients with an HCC history.

Key Words: direct acting antivirals; hepatitis C virus; hepatocellular carcinoma; recurrence; liver fibrosis; curative treatment

Tajiri K, Ito H, Kawai K, Kashii Y, Hayashi Y, Murayama A, Minemura M, Takahara T, Shimizu Y, Yasuda I. Direct-acting antivirals for HCV-infected patients with hepatocellular carcinoma. *World J Hepatol* 2022; In press

Core Tip: To estimate the therapeutic value of direct-acting antivirals (DAA) for hepatitis C virus (HCV) infected patients with a history of hepatocellular carcinoma (HCC), we retrospectively analyzed the clinical course of HCV patients with or without a history of HCC after DAA-therapy. The incidence rate of HCC (re)occurrence was not increased by DAA-therapy. Malignant transformation of HCC by DAA-therapy was not observed in patients with a history of HCC. The risk of HCC recurrence after DAA-therapy was determined by comparison with the frequency of HCC (re)occurrence before DAA-therapy.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the major malignancies known to cause substantial cancer-related mortality in the world. If HCC is detected at an early stage, it can be cured by surgical resection or local ablative therapy. However HCC is often found at an advanced stage, which leads to its high mortality[1]. Viral hepatitis is associated with the development of HCC, and hepatitis C virus (HCV) infection is the major etiology of HCC even though the number of cases with non-viral etiologies such as nonalcoholic fatty liver disease have been increasing[2]. HCV-related HCC often recurs after curative therapies for HCC such as surgical resection or ablative therapies and has a 5-year 60-80% recurrence rate[3]. Therefore, measures for HCV-related HCC have been explored to date.

Interferon-based HCV eradication was reported to decrease HCC incidence rate[4]. Decreased numbers of cases with liver inflammation due to HCV eradication and the anti-carcinogenic effect of interferon have contributed to the decrease of HCC (re)occurrence. However, it has been debated that there may be increased HCC risk by HCV eradication with direct-acting antivirals (DAA). Disruption of immune surveillance by DAA-therapy for rapid HCV elimination had been suggested[5]. But larger-scale studies showed that HCV eradication with DAA-therapy did not lead to increased risk of HCC, whereas basal liver fibrosis was associated with risk of HCC[6-8]. However, since some previous studies showed malignant transformation by HCV eradication with DAA-therapy suggesting adverse carcinogenic effects of DAA-therapy[5, 9], such carcinogenic risks should be especially considered in patients with a history of HCC. The significance of DAA-therapy for patients with an HCC history has therefore been explored. Previous studies suggested that pre-existing malignant potential such as advanced liver fibrosis, high alpha-fetoprotein (AFP) value or presence of precancerous nodules, might lead to HCC recurrence in patients with an HCC history[10-14].

In the present study, we retrospectively evaluated the (re)occurrence (a coined term to include recurrence in patients with an HCC history and/or occurrence in those without an HCC history) rate of HCC and the clinical course of HCC in HCV patients that

underwent DAA-therapy. Our study implied that pre-DAA-therapy history of HCC is the major factor contributing to post-DAA-therapy HCC (re)occurrence.

MATERIALS AND METHODS

Patients

HVC patients treated at Toyama University Hospital, Takaoka Municipal Hospital, Nanto Municipal Hospital, and Saiseikai Toyama Hospital, who received DAA-therapy between November 2014 and July 2020, were enrolled. HCV infection was confirmed by HCV-RNA quantification and the genotype of HCV was determined in all patients. The Fib-4 index, a useful noninvasive method for assessment of liver fibrosis[15], was also evaluated in all patients. Hepatologists, each with over 20 years' of experience, made the diagnoses of liver cirrhosis using imaging such as ultrasonography (US), computed tomography (CT), elastography and the titer of fibrosis markers such as platelet count, Fib-4 index, or other fibrosis markers. Diagnoses of HCC were made from histological or imaging data such as contrast-enhanced CT or magnetic resonance imaging (MRI) according to criteria of the American Association for the Study of Liver Diseases diagnosis guidelines[16]. Before DAA-therapy, all patients were screened using US, CT, or MRI to rule out any presence of viable HCC. This multicenter study accorded with the 1975 Declaration of Helsinki and was approved by Toyama University Ethics Committee (Approved number: R2019-131).

Treatment with direct-acting antivirals

Before DAA-therapy, HCC had been treated by surgery, radiofrequency ablation (RFA), or trans-arterial chemoembolization (TACE) in patients with viable HCC. Patients who did not show viable HCC lesions in contrast-enhanced CT or MRI examination performed 1 to 3 mo after the aforementioned treatment were considered eligible for DAA-therapy. Treatment regimens were determined by respective hepatologists according to guidelines for HCV treatment[17, 18]. Daclatasvir plus asunaprevir (DCV+ASV) regimen was considered for patients with genotype 1b from 2014 to 2016.

Sofosbuvir plus ledipasvir regimen (SOF+LDV) was considered for patients with genotype 1b and 2a/2b from 2015 to 2020. Sofosbuvir plus ribavirin regimen (SOF+Rib) was considered for patients with genotype 2a/2b from 2015 to 2017. Glecaprevir and pibrentasvir regimen (GLE+PIB) was considered for patients with any genotype from 2017 to 2020. Ombitasvir, paritaprevir and ritonavir regimen (2016-2017), elbasvir and grazoprevir regimen (2017) or SOF and velpatasvir regimen (2019-2020) were also considered according to patient condition and timing of treatment. During DAA-therapy, patients were followed-up every 4 wk, and afterwards every 12 wk, with evaluation for HCC by imaging studies. Sustained viral response (SVR) was determined with HCV-RNA clearance at 12 wk after DAA-therapy. The flow chart of this study is shown in supplementary figure 1. The median observation period after DAA therapy was 1,311 (range: 28 to 2,231) days.

HCC Treatment

HCC treatment in each patient was determined through discussion among surgeons, hepatologists, and radiologists, at each institution based on Japanese practice guidelines for HCC[19]. For early-stage HCC, surgical resection or RFA were considered. For multiple HCC, TACE or systemic chemotherapy such as sorafenib were considered, according to liver function and tumor progression, following treatment guidelines.

Statistical analyses

Variable distributions were documented as mean ± standard deviation (SD). Categorical variables were compared by Fisher's exact test. Continuous variables were compared by Student's t-test or Mann-Whitney test. Survival analyses were evaluated using the Kaplan-Meier method, and differences in the survival curve were compared by log-rank test. Person-years method was used to determine incidence rates of HCC (re)occurrence Differences with a $p<0.05$ were deemed significant. All analyses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients and (re)occurrence of HCC

Of the 311 patients included in the study (Table 1), 168 (54.0%) were female. Among the 311 patients, 87 (28.0%) were cirrhosis and 229 (73.6%) were genotype 1b. Fib-4 index was 3.87 ± 3.24 and AFP was 12.0 ± 35.2 ng/mL (mean ± SD). The group of 53 patients with an HCC history showed higher age (75.6 *vs* 66.5 yrs. p<0.01), more diabetes, also known as a risk factor of HCC after DAA-therapy[20] (35.8 *vs* 3.1%, p<0.01), more liver cirrhosis (34.0 *vs* 20.2%, p<0.01), fewer genotype 2 (13.2 *vs* 25.6%, *P* = 0.04), lower serum albumin (3.5 *vs* 4.0 g/dL, p<0.01), lower platelet (12.9 *vs* 16.7x10^4/mL, *p*<0.01), higher Fib-4 index (6.27 *vs* 3.37, p<0.01) and higher AFP (23.7 *vs* 9.4 ng/mL, *p*=0.047). Patients with habitual alcohol use were found in 21.9% (56/311) of patients, and no significant difference was found whether with or without HCC. Thus patients with, than without, an HCC history were older and had more advanced liver fibrosis progression and diabetes.

Treatment with direct-acting antivirals

HCV patients with genotype 1b were administered DCV+ASV, SOF+LDV, GLE+PIB, or other regimens in accordance with contemporary guidelines. Likewise, those with genotype 2a/2b were administered SOF+Rib, SOF+LDV, GLE+PIB, or others. GLE+PIB regimens were administered to patients with other genotypes such as 3a/3b/4. In the present study, SVR was achieved in 98.1% (52/53 cases) of patients with an HCC history and 96.9% (250/258 cases) in patients without, showing no significant between group difference (*p*=1.00). A few cases that did not initially achieve SVR were switched to another DAA and thus SVR was achieved in all treated cases. Post-DAA-therapy AFP levels in patients with, than without, an HCC history at both EOT and SVR were higher, albeit lower than their respective pre-DAA-therapy levels (Table 2).

HCC after DAA-therapy

Post-DAA-therapy HCC (re)occurrence was found in 29 patients (53.7%) with and 5 patients (1.9%) without an HCC history with 3-year incidence rates of 50.9% (27/53 cases) and 1.2% (3/258 cases), respectively. The median RFS in patients with an HCC history was 1092 days, whereas none of those without an HCC history died during the 6-year study period ($p<0.001$, Figure 1). HCC (re)occurrence was more frequent in patients with, than without, an HCC history.

HCC both before and after DAA-therapy

Respective pre- and post-DAA-therapy HCC recurrence and other parameters were compared in patients with an HCC history. No significant difference was found in RFS (Median RFS: 1293 (554-2032) and 1053 (741-1443) days, $P = 0.884$) (Figure 2A). The pre- and post-DAA-therapy incidence rates of HCC recurrence were 1/1.25 and 1/2.99 person-years, respectively (Figure 2B). DAA-therapy induced HCV clearance did not increase HCC recurrence. In univariate analysis of HCC recurrence, AFP value at SVR and frequency of pre-DAA-therapy HCC recurrence were risk factors of post-DAA-therapy HCC recurrence. In multivariate analysis, only frequency of pre-DAA-therapy HCC recurrence was an independent predictive factor of post-DAA-therapy HCC recurrence (Table 3). HCV clearance by DAA-therapy alone did not increase the risk of post-DAA-therapy HCC recurrence. Only history of pre-DAA-therapy HCC contributed to the risk. In patients with only 1 prior HCC event, the risk of post-DAA-therapy HCC recurrence was relatively lower than in those with multiple prior events (1-year recurrence rate in patients with 1, 2, and ≥3 pre-DAA-therapy HCC events: 28%, 40% and 38.5%, respectively) (Figure 3).

Clinical course after HCC recurrence

All 29 patients with an HCC history that showed HCC recurrence after DAA-therapy had been treated using treatment modalities in accordance with a guideline for HCC treatment[19]. Surgical resection and RFA was performed in 6 and 17 patients, respectively. Multiple recurrence was observed in 6 patients among whom portal

invasion was observed in 1 patient. The 6 patients were subsequently treated with TACE, hepatic artery infusion chemotherapy, or sorafenib. Two of the 6 died due to advanced HCC, with survival times following DAA-therapy completion of 49.7 and 52.6 mo, respectively.

DISCUSSION

In the present study, HCV eradication by DAA-therapy did not increase the risk of HCC recurrence. Only prior history of HCC was found to be an independent factor to predict the risk of post-DAA-therapy HCC recurrence among several factors assessed by multivariate analysis. However DAA-therapy did not worsen the clinical course of subsequent HCC events. Rather the liver reserve function was preserved, and curative and continuous treatment of HCC could be achieved. Although malignant transformation after DAA-therapy has been reported[5, 9], the present study did not suggest DAA-therapy *per se* as the causal agent.

In the present study, the SVR rate was 98.1% in patients with, and 96.9% in those without, an HCC history. Previous systematic reviews have reported lower SVR rates in patients with an HCC history[21]. If curative treatment was achieved, DAA-therapy was extremely effective to eradicate HCV in patients with an HCC history, even though they were old and had liver fibrosis and diabetes mellitus. Recently, the effectiveness of DAA-therapy has been shown also in patients with advanced HCC[22-24]. HCV eradication by DAA-therapy ameliorates liver inflammation and suppresses liver fibrosis progression efficiently, leading to preserved or improved liver function. Since the introduction of DAA-therapy as a treatment for HCV, HCV-HCC mortality has improved compared with HBV related HCC or non-viral HCC[25]. Thus HCV eradication might contribute to prolong overall survival also in patients with HCC.

On the other hand, increased risk of HCC after HCV eradication by DAA-therapy has been discussed. However, most studies suggested preexisting risk factors for HCC development were present at time of DAA initiation. Firstly, progression of liver fibrosis or presence of cirrhosis have been shown to be associated with HCC

development[6-8]. Chronic HCV infection leads to liver fibrosis progression, the most contributing factor of HCC development through various epigenetic changes and formation of a microenvironment favorable to carcinogenesis[26]. A recent study showed that increased risk of HCC (re)occurrence after DAA-therapy was found in patients with, than without, advanced liver fibrosis[27]. Therefore earlier SVR achievement before fibrosis development may lead to a lower likelihood of HCC (re)occurrence. Second, the value of AFP as a predictor of HCC development has also been described[10, 13]. Higher AFP has been widely recognized as a major biomarker for HCC occurrence after SVR[28, 29]. AFP increase is known to be associated with not only HCC but liver inflammation. Therefore consideration to the value of AFP at treatment completion is important[30]. It is important to consider AFP measurement both before and after DAA-therapy to estimate the risk of HCC (re)occurrence. Third, presence of preexisting hepatic nodules for HCC development has also been discussed[14]. In the present study, all patients who received DAA-therapy were evaluated with imaging studies. However, enhanced CT or MRI were not performed in all of the patients, so the exact proportion of patients with dysplastic nodules was unclear. A patient with a 1.5 cm dysplastic nodule in the liver who had been evaluated with ethoxybenzyl-diethylenetriamine pentaacetic acid enhanced (EOB)-MRI, developed HCC from the dysplastic nodule 3-years after DAA completion, akin to hypervascular transformation of 9 mm hypovascular nodules with a 3-year incidence rate of 30%[31]. A recent study showed certain types of DAA, such as SOF and DCV, enhance oncogenic potential through off-target DAA effects[32]. In the present study, HCC (re)occurrence was not frequent in patients treated with SOF or DCV (data not shown). Collectively, DAA-therapy in patients with an HCC history was effective because SVR showed elimination of hepatic inflammation and suppression of hepatic fibrosis advancement, leading to preserve liver function. Improvement or preservation of liver function is really favorable in the management of HCC. Further prospective studies are required to evaluate the risk of transformation into HCC of precancerous lesions by DAA-therapy or risk of HCC (re)occurrence by type of DAA.

In the present study, neither liver fibrosis, nor diabetes mellitus, or AFP value before DAA-therapy were significantly associated with HCC (re)occurrence after DAA-therapy according to multivariate analysis. Only history of prior HCC events was a significant factor in post-DAA-therapy HCC recurrence. One should consider risk of HCC (re)occurrence especially in patients with an HCC history. Recently the effectiveness of DAA-therapy has been suggested in patients with multiple prior courses of HCC recurrence[33]. Therefore careful pre-DAA-therapy HCC screening is required in patients with an HCC history, with similar diligent follow-up attention paid to these patients after DAA-therapy. In such patients, estimation of the risk for HCC after DAA treatment is important and the degree of liver fibrosis is an essential factor to predict HCC recurrence[34, 35]. A recent study suggested that previous HCC history in addition to stratification with Fib-4 index is a novel standard predictive model for HCC development after DAA treatment[36]. Thus more cautious screening before DAA treatment and more emphasis on follow-up is required in patients with an HCC history according to the number of times they have experienced HCC recurrence.

This study has several limitations. First, since it was retrospective, we could not assess an accurate risk of HCC (re)occurrence by DAA-therapy. Second, the number of patients included in the present study was relatively small. Especially, the number of patients with an HCC history of multiple events was limited. Third, the actual HCC or non-HCC status of patients might be uncertain because EOB-MRI was not performed in all participants. Although enhanced CT or US by experienced hepatologists were performed instead of EOB-MRI, further studies are required to evaluate HCC precisely regarding the possibility of involved precancerous lesions. Furthermore patient data on other known risk factors for HCC, including tobacco use, obesity, and metabolic diseases, *etc.*, were not available for analysis.

CONCLUSION

DAA-therapy in patients with HCV infection is a useful treatment option to preserve liver function also in patients with HCC. Curative treatment of HCC is desirable before

DAA-therapy. A history of multiple courses of HCC events before DAA-therapy significantly increased the risk of HCC recurrence. Careful HCC screening prior to DAA-therapy and thorough follow-up observation after DAA-therapy is recommended in such patients.

ARTICLE HIGHLIGHTS

Research background

Direct-acting antivirals (DAAs) treatment has been developed and provides many benefits for hepatitis C virus (HCV)-infected patients. But hepatocellular carcinoma (HCC) development after DAAs treatment is a serious issue.

Research motivation

It is an important clinical question whether the risk of HCC development increase or not after DAAs treatment.

Research objectives

To clarify the risk of HCC development after DAAs treatment in patients with high risk for HCC development.

Research methods

We retrospectively evaluated HCC occurrence after DAAs treatment in patients with or without HCC history.

Research results

The frequency of HCC (re)occurrence was similar between before and after DAAs treatment. The number of HCC occurrence before DAAs treatment was an independent risk factor of HCC (re)occurrence.

Research conclusions

HCV patients with multiple history of HCC occurrence should be observed carefully for HCC recurrence.

Research perspectives

Effective screening way for such patients with high risk of HCC (re)occurrence should be established.

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