Dai *et al. Hepatoma Res* 2020;6:16
DOI: 10.20517/2394-5079.2019.40

Hepatoma Research

Original Article

Open Access

Treatment efficacy for patients with chronic hepatitis C and preexisting hepatocellular carcinoma by directly acting antivirals

Chia-Yen Dai[1-4], Chung-Feng Huang[1,3,4], Meng-Hsuan Hsieh[1,2], Ching-I Huang[1], Ming-Lun Yeh[1,3], Pei-Chien Tsai[1], Ching-Chih Lin[1], Meng-Szu Lee[2], Jeng-Fu Yang[1,2], Po-Yao Hsu[1], Yu-Ju Wei[1], Cheng-Ting Hsu[1], Po-Cheng Liang[1], Yi-Hung Lin[1], Jee-Fu Huang[3,4], Wan-Long Chuang[3,4], Ming-Lung Yu[1,3,4]

[1]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan.
[2]Health Management Center & Department of Community Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan.
[3]Faculty of Internal Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan.
[4]Department of Biological Science and Technology, College of Biological Science and Technology, National Chiao Tung University, Hsin-Chu, Kaohsiung 807, Taiwan.

Correspondence to: Dr. Ming-Lung Yu, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100, Shi-Tzyou 1st Road, Kaohsiung 807, Taiwan. E-mail: fish6069@gmail.com

How to cite this article: Dai CY, Huang CF, Hsieh MH, Huang CI, Yeh ML, Tsai PC, Lin CC, Lee MS, Yang JF, Hsu PY, Wei YJ, Hsu CT, Liang PC, Lin YH, Huang JF, Chuang WL, Yu ML. Treatment efficacy for patients with chronic hepatitis C and preexisting hepatocellular carcinoma by directly acting antivirals. *Hepatoma Res* 2020;6:16. http://dx.doi.org/10.20517/2394-5079.2019.40

Received: 2 Dec 2019 **First Decision:** 13 Feb 2020 **Revised:** 23 Mar 2020 **Accepted:** 27 Mar 2020 **Published:** 10 Apr 2020

Science Editor: Guang-Wen Cao **Copy Editor:** Jing-Wen Zhang **Production Editor:** Tian Zhang

Abstract

Aim: Despite the high cure rate of interferon-free directly acting antivirals (DAAs) for chronic hepatitis C (CHC) patients, the treatment efficacy for patients with preexisting hepatocellular carcinoma (HCC) remains undefined. We aimed in the present study to address the issue by using novel DAAs in treating CHC patients who were adherent to treatment in Taiwan.

Methods: CHC patients with or without HCC were consecutively enrolled. The primary objective was sustained virological response (SVR) defined as undetectable HCV RNA throughout 12 weeks of a post-treatment follow-up period (SVR12). Only patients with available SVR12 were enrolled for final analysis.

Results: A total of 1237 patients (1113 non-HCC, 101 inactive HCC and 23 active HCC) were enrolled. The overall SVR12 rate was 98.9%, and was similar between HCV patients with and without pre-existing HCC (98.4% *vs.* 98.9%, $P = 0.64$). While HCC patients were classified as those who had active or inactive HCC, the SVR12 was also similar between patients with and without active HCC (95.7% *vs.* 99.0%, $P = 0.34$). Among the 101 patients without viable HCC at the time of DAA initiation, eighty-four patients exhibited curative therapy and the other 17

patients experienced HCC recurrence before DAAs. Among the 23 patients with viable HCC at the time of DAA treatment, 10 patients had received curative therapy for HCC whereas the remaining 13 patients had HCC that was never cured. The SVR12 rates were also similar among the four subpopulations, being 98.8% (83/84), 100% (17/17), 90% (9/10) and 100% (13/13) respectively.

Conclusion: CHC patients with HCC who were adherent to potent DAAs achieved similar SVR12 rate compared to those without HCC and could be effectively treated.

Keywords: Directly acting antiviral, chronic hepatitis C, hepatitis C virus, hepatocellular carcinoma, sustained virological response

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies[1], which attributes to the second cause of cancer-related death worldwide[2]. Hepatitis C virus (HCV) infection is one of the leading etiologies of HCC, which may account for one third of HCC patients[3]. On the other hand, the risk of HCC decreases drastically after successful antiviral therapy[4]. Interferon-free all oral directly acting antivirals (DAAs) have become a standard of care since 2014, providing ultimately high HCV cure rate and satisfactory safety profiles[5,6]. Emerging evidence has also shown the benefit of DAAs in reducing the development of HCV-related HCC[7].

Recently, the issue concerning whether pre-existing HCC would compromise the sustained virological response (SVR) rate in chronic hepatitis C (CHC) patients with DAAs has been raised, although discordant results might in part be attributed to different treatment regimens and patient characteristics[8]. In patients with pre-existing HCC, a recent meta-analysis has shown that different treatment responses might exist between patients with or without viable HCC at the time of initiating DAAs[9]. Some of the earlier studies used suboptimal treatment regimens that could not truly reflect the real world situation nowadays[10]. By using current DAAs, an SVR rate of > 95% could be accomplished across populations[11,12]. It is therefore crucial to revisit the issue by using potent DAAs in daily practice. In addition, HCC patients might have more safety concerns and are more likely to have experienced treatment discontinuation[5]. Unequal tolerability might further compromise efficacy evaluation in these patients. Herein, we aimed to explore the issue by recruiting a well-characterized patient group in terms of HCC status who were adherent to novel DAA regimens.

METHODS

Patients receiving DAAs were consecutively enrolled from Aug 2015 to Mar 2019. The treatment strategies were based on regional guidelines[13] and regulations of the Ministry of Health and Welfare of Taiwan. Daclatasvir (DCV)/Asunaprevir (ASV) for HCV genotype 1 (HCV-1) and Sofosbuvir (SOF)/ribavirin for HCV-2 have been reimbursed in Taiwan since 2017. Due to the previous relatively suboptimal treatment responses, patients who used these regimens were excluded in the current study.

The diagnosis of HCC was ascertained by pathology or clinical judgments based on the guidelines of the Asian Pacific Association for the Study of the Liver[14] and the American Association for the Study of Liver Diseases[2]. HCC was defined as curative if the initial presentation could be managed by surgical resection, local ablation or liver transplantation. The inactive HCC indicated that patients who had non-viable HCC were defined as if there were no image evidence of recurrence within 6 months before initiating DAA treatment. Other patients were defined with active HCC. The Review Board of the Kaohsiung Medical University Hospital approved the protocols that followed the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients provided written informed consent.

Table 1. Basic characteristics and treatment regimens of the patients with or without HCC

	All patients (*n* = 1237)	Non-HCC (*n* = 1113)	HCC (*n* = 124)	*P* value
Male gender, *n* (%)	542 (43.8)	477 (42.9)	65 (52.4)	0.04
Age, years (mean ± SD)	61.8 ± 11.8	61.1 ± 11.8	68.5 ± 9.4	< 0.001
Body weight, kg (mean ± SD)	63.7 ± 12.4	64.0 ± 12.5	61.0 ± 10.7	0.005
Diabetes, *n* (%)	273 (22.1)	244 (21.9)	29 (23.4)	0.71
Hypertension, *n* (%)	502 (40.6)	446 (40.1)	56 (45.2)	0.27
Platelet count, × 1000/mm^3 (mean ± SD)	170 ± 70	173 ± 68	144 ± 84	< 0.001
AST, IU/L (mean ± SD)	68.4 ± 48.0	67.1 ± 45.6	79.6 ± 49.9	0.009
ALT, IU/L (mean ± SD)	77.6 ± 64.4	77.7 ± 65.3	76.8 ± 56.4	0.88
Serum albumin, g/dL (mean ± SD)	4.3 ± 0.4	4.3 ± 0.4	4.0 ± 0.5	< 0.001
Serum bilirubin, mg/dL (mean ± SD)	1.0 ± 0.5	1.0 ± 0.5	1.1 ± 0.6	0.009
FIB-4 (mean ± SD)	3.80 ± 3.47	3.60 ± 3.39	5.62 ± 3.71	< 0.001
HCV RNA, log IU/mL	5.65 ± 1.01	5.67 ± 1.01	5.49 ± 0.99	0.06
HCV genotype, *n* (%)				
1	923 (74.6)	824 (74.0)	99 (79.8)	0.16
Non-1	314 (25.4)	289 (26.0)	25 (20.0)	
Liver cirrhosis, *n* (%)	597 (48.3)	516 (46.4)	81 (65.3)	< 0.001
Decompensation, *n* (%)	28 (4.7)	20 (3.9)	8 (9.9)	0.04
Prior treatment experienced*, *n* (%)	335 (27.1)	286 (25.7)	49 (39.5)	0.001
HBsAg (+), *n* (%)	83 (6.7)	74 (6.6)	9 (7.3)	0.8
HIV (+), *n* (%)	19 (1.5)			
PWID				0.64
Past usage	31 (2.5)	29 (2.6)	2 (1.6)	
Current usage	4 (0.3)	4 (0.4)	0 (0)	
Regimen, *n* (%)				0.03
PrOD ± RBV	423 (34.2)	370 (33.2)	53 (42.7)	
SOF/LDV ± RBV	338 (27.3)	309 (27.8)	29 (23.4)	
SOF/DCV ± RBV	122 (9.9)	105 (9.4)	17 (13.7)	
ELB/GRZ	157 (12.7)	141 (12.7)	16 (12.9)	
GLE/PIB	193 (15.6)	184 (16.5)	9 (7.3)	
SOF/VEL	4 (0.3)	4 (0.4)	0 (0)	
Sustained virological response, *n* (%)	1223 (98.9)	1101 (98.9)	122 (98.4)	0.64

AST: aspartate aminotransferase; ALT: alanine aminotransferase; FIB-4: fibrosis-4 index; HBsAg: hepatitis B surface antigen; PWID: patients who inject drugs; HIV: human immunodeficiency virus; PrOD: Paritaprevir/ritonavir/Ombitasvir/Dasabuvir; DCV: Daclatasvir; SOF: Sofosbuvir; LDV: Ledipasvir; ELB: Elbasvir; GRZ: Grazoprevir; VEL: Velpatasvir; GLE: Glecaprevir; PIB: Pibrentasvir; RBV: ribavirin; HCC: hepatocellular carcinoma. *All interferon-based therapy

The primary outcome was treatment efficacy defined as undetectable HCV RNA at the 12-week follow-up period after completing the anti-HCV therapy (SVR12). Only patients with available SVR12 were enrolled for final analysis.

The HCV RNA and HCV genotypes were tested by using real-time PCR assay (RealTime HCV; Abbott Molecular, Des Plaines IL, USA; with the detection limit: 12 IU/mL)[15] defined by any of the following: liver histology[16], transient elastography (FibroScan®; Echosens, Paris, France) > 12 kPa[17], acoustic radiation force impulse (> 1.98 m/s)[18], fibrosis-4 index (FIB-4, > 6.5)[19] and/or the presence of clinical, radiological, endoscopic, or laboratory evidence of cirrhosis and/or portal hypertension.

Statistical analyses

Frequency was compared between groups using the χ^2 test with the Yates correction or Fisher's exact test. Group means (presented as the mean standard deviation) were compared using analysis of variance and Student's *t*-test or the nonparametric Mann-Whitney test when appropriate. The fibrosis-4 score (FIB-4) was calculated as age (years) × AST (U/L)/{platelets (10^9/L) × [alanine transaminase (ALT) (U/L)]}$^{1/2}$. The statistical analyses were performed by using the SPSS 12.0 statistical package (SPSS, Chicago, IL, USA). All the statistical analyses were based on two-sided hypothesis tests with a significance level of $P < 0.05$.

RESULTS

Patient characteristics

As shown in Table 1, 1237 patients were enrolled in the current study, with their patient and viral characteristics and treatment regimens also shown. The mean age was 61.8 years with 43.8% being males; the most common viral genotype was HCV genotype-1 (HCV-1, 74.6%); and the proportion of patients with liver cirrhosis was 48.3% (n = 597), whereas 28 patients (4.7%) had decompensated liver cirrhosis. Three hundred and thirty-five patients (27.1%) failed previous interferon-based regimens, and 83 patients (6.7%) were dually infected with the hepatitis B virus. The most commonly used DAA regimen was Paritaprevir/ritonavir plus Ombitasvir and Dasabuvir (PrOD) (34.2%), followed by SOF plus Ledipasvir (LDV).

One hundred and twenty-four patients (10.0%) had previous history of HCC before treatment. Of them, 101 patients (8.2%) had inactive HCC whereas the remaining 23 patients (1.9%) had active HCC at the time of DAA initiation.

Compared to patients without HCC, those with pre-existing HCC were older, had higher pretreatment aspartate aminotransferase, FIB-4 and bilirubin levels, lower body weight, albumin and platelet counts, and a higher proportion were males, had liver cirrhosis, and interferon-experienced history. Treatment regimens differed among patients with or without HCC; HCC patients had a higher proportion of PrOD usage than those without.

Treatment responses

The SVR12 rate was 98.9%, and was 99.3%, 98.7%, 97.9%, 100%, 99% and 100% in patients who received PrOD, Elbasvir (EBR)/Grazoprevir (GZR), SOF/LDV, SOF/DCV, Glecaprevir (GLE)/Pibrentasvir (PIB) and SOF/Velpatasvir (VEL) respectively. The SVR12 was similar between patients with and without pre-existing HCC (98.4% *vs.* 98.9%, P = 0.64) [Table1]. While HCC patients were classified as those with active or inactive HCC, the SVR12 was also similar between patients with and without active HCC (95.7% *vs.* 99.0%, P = 0.34).

Among the 101 patients without viable HCC at the time of DAA initiation, eighty-four patients were with curative therapy and the other 17 patients experienced HCC recurrence before DAAs. Among the 23 patients with viable HCC at the time of DAA treatment, ten patients with HCC had ever received curative therapy whereas the remaining 13 patients with HCC had never received this. Patient and viral characteristics as well as treatment regimens are shown in Table 2. The SVR12 rates were similar among the four populations, being 98.8% (83/84), 100% (17/17), 90% (9/10) and 100% (13/13) respectively. None of the clinical factor including the HCC status was associated with SVR to the DAA treatment [Table 3].

DISCUSSION

In the present study in Taiwanese patients with HCC, in addition to the similar effectiveness compared to patients without HCC by high potency DAAs, we demonstrate equivalent effectiveness also in both patients with and without HCC. With a relatively high SVR rate by interferon-based therapy in Taiwan compared to Western countries[20,21], the Taiwanese National Health Insurance Scheme has reimbursed the cost of the PegIFN/RBV therapy since 2013[22]. Due to the adverse effects of the IFN-based regimen, the treatment of patients with HCC is quite limited, even though the SVR rate is equivalent in patients with and without HCC when patients achieved good adherence, particularly in CHC patients after successful eradication of HCC[23]. Since 2017, DAAs have been reimbursed by TNHI (free of charge for DAA medication) in patients with limited to advanced fibrosis and cirrhosis. The DAA treatment then became the standard treatment of CHC in Taiwan for patients fulfilling the reimbursement criteria, instead of interferon-based therapy. The high SVR rate has been reported as more than 97% in patients who completed the duration of therapy by ASV plus DCV if the patients had no NS5A mutants, PrOD with/without RBV and GZR/EBR with/without

Table 2. Characteristics of patient with HCC history and cancer status at the time of DAA treatment

	Inactive HCC		Active HCC	
	Curative & non-viable (*n* = 84)	Recurrent & non-viable (*n* = 17)	Once curative & viable (*n* = 10)	Never curative & viable (*n* = 13)
Male gender, *n* (%)	40 (47.6)	11 (64.7)	6 (60)	8 (61.5)
Age, years (mean ± SD)	68.8 ± 9.9	67.8 ± 7.3	70.2 ± 8.3	66.6 ± 9.7
Body weight, kg (mean ± SD)	60.7 ± 10.5	59.9 ± 10.9	61.9 ± 12.8	63.8 ± 11.1
Diabetes, *n* (%)	15 (17.9)	8 (47.1)	2 (20)	4 (30.8)
Hypertension, *n* (%)	39 (46.4)	8 (47.1)	5 (50.0)	4 (30.8)
Platelet count, × 1000/mm^3 (mean ± SD)	146 ± 94	140 ± 53	152 ± 55	135 ± 65
AST, IU/L (mean ± SD)	82.3 ± 56.1	72.9 ± 36.7	71.5 ± 34.7	77.2 ± 29.8
ALT, IU/L (mean ± SD)	77.3 ± 59.7	71.6 ± 48.8	77.6 ± 59.8	80.3 ± 45.8
Serum albumin, g/dL(mean ± SD)	4.0 ± 0.5	3.9 ± 0.5	4.1 ± 0.3	3.9 ± 0.6
Serum bilirubin, mg/dL (mean ± SD)	1.1 + 0.5	1.0 ± 0.4	1.0 + 0.5	1.3 + 0.9
FIB-4 (mean ± SD)	5.77 ± 3.73	5.31 ± 3.84	4.49 ± 2.47	5.93 ± 4.41
HCV RNA, log IU/mL	5.50 ± 1.00	5.51 ± 0.93	5.48 ± 0.97	5.40 ± 1.07
HCV genotype 1, *n* (%)	70 (83.3)	13 (76.5)	6 (60.0)	10 (76.9)
Liver cirrhosis, *n* (%)	54 (64.3)	10 (58.8)	6 (60.0)	11 (84.6)
Decompensation, *n* (%)	5 (6.0)	1 (5.9)	0 (0)	2 (15.4)
Prior treatment experienced*, *n* (%)	36 (42.9)	4 (23.5)	5 (50.0)	4 (30.8)
HBsAg (+)	3 (3.6)	5 (29.4)	1 (10.0)	0 (0)
PrOD ± RBV	42 (50.0)	3 (17.6)	5 (50.0)	3 (23.3)
SOF/LDV ± RBV	22 (26.2)	3 (17.6)	1 (10.0)	3 (23.3)
SOF/DCV ± RBV	8 (9.5)	4 (23.5)	3 (30.0)	2 (15.4)
ELB/GRZ	6 (7.1)	6 (35.3)	1 (10.0)	3 (23.3)
GLE/PIB	6 (7.1)	1 (5.9)	0 (0)	2 (15.4)
Sustained virological response, *n* (%)	83 (98.8)	17 (100)	9 (90)	13 (100)

HCC: hepatocellular carcinoma; DAA: directly acting antivirals; AST: aspartate aminotransferase; ALT: alanine aminotransferase; FIB-4: fibrosis-4 index; HBsAg: hepatitis B surface antigen; PrOD: Paritaprevir/ritonavir/Ombitasvir/Dasabuvir; DCV: Daclatasvir; SOF: Sofosbuvir; LDV: Ledipasvir; ELB: Elbasvir; GRZ: Grazoprevir; VEL: Velpatasvir; GLE: Glecaprevir; PIB: Pibrentasvir; RBV: ribavirin. *All interferon-based therapy

RBV[24]. Since 2019, patients with all stages of fibrosis have been reimbursed for DAA therapy, and all high potency first-line DAAs are available. The treatment of CHC has come to a new era including all subgroups of patients including patients with HCC particularly in patients with liver function impairment with the administration of new agents with SOF/LDV or SOF/VEL but not protease inhibitors.

The cure for HCV in HCC patients is encouraged by association with increased overall survival in these patients by interferon-based therapy, as per reports by Singal *et al.*[25] and Morgan *et al.*[26] Recently the benefits of the eradication of HCV infection by DAAs have also been elucidated by Kamp *et al.*[27] and Dang *et al.*[28] Nevertheless, the potentially suboptimal antiviral treatment efficacy by DAAs has been reported by some studies indicating treatment inferiority for HCC patients. Beste *et al.*[29] reported the presence of HCC being associated with lower likelihood of SVR with SOF, SOF/LDV, and PrOD with or without ribavirin. Saberi *et al.*[10] have observed a high rate of viral relapse after DAA treatment in patients with a concurrent HCC diagnosis in their case series. Prenner *et al.*[30] have reported that when considering the treatment efficacy, presence of active HCC at the initiation of HCV therapy is significantly associated with DAA treatment failure. Radhakrishnan *et al.*[31] reported the presence of HCC was associated with significantly lower odds of achieving SVR compared to those who had no HCC. However, HCC treatment status was not associated with SVR among those with HCC.

A recent meta-analysis including 49 studies from 15 countries concluded that compared to those without HCC, SVR rates were lower in patients with HCC, especially with active HCC[9]. Patients with HCC treated with SOF/LDV had lower SVR rates than patients without HCC (92.6%, n = 884 *vs.* 97.8%, P = 0.026) and active/residual HCC than patients with inactive/ablated HCC (SVR 73.1% *vs.* 92.6%, P = 0.002). The role of

Table 3. Factors associated with SVR

	Non-SVR (*n* = 14)	SVR (*n* = 1223)	*P* value
Male gender, *n* (%)	8 (57.1)	534 (43.7)	0.31
Age, years (mean ± SD)	58.8 ± 11.3	61.9 ± 11.8	0.33
Body weight, kg (mean ± SD)	70.9 ± 16.8	63.3 ± 12.3	0.13
Diabetes, *n* (%)	3 (21.4)	270 (22.1)	1.00
Hypertension, *n* (%)	3 (21.4)	499 (40.8)	0.14
Platelet count, × 1000/mm^3 (mean ± SD)	176 ± 79	170 ± 70	0.77
AST, IU/L (mean ± SD)	79.8 ± 58.0	68.2 ± 47.8	0.47
ALT, IU/L (mean ± SD)	86.8 ± 52.9	77.5 ± 64.6	0.53
Serum albumin, g/dL (mean ± SD)	4.3 ± 0.5	4.3 ± 0.4	0.48
Serum bilirubin, mg/dL (mean ± SD)	1.1 ± 0.5	1.0 ± 0.5	0.34
FIB-4 (mean ± SD)	5.08 ± 7.21	3.79 ± 3.41	0.17
HCV RNA, log IU/mL	5.88 ± 0.97	5.65 ± 1.01	0.40
HCV genotype 1, *n* (%)	10 (71.4)	913 (74.7)	0.76
Liver cirrhosis, *n* (%)	5 (35.7)	592 (48.4)	0.43
Decompensation, *n* (%)	0 (0)	28 (0.2)	1.00
Prior treatment experienced*, *n* (%)	4 (28.6)	331 (27.1)	1.00
HBsAg (+)	0 (0)	83 (6.8)	0.62
Regimen, *n* (%)			0.44
PrOD ± RBV	3 (21.4)	420 (34.3)	
SOF/LDV ± RBV	7 (50.0)	331 (27.1)	
SOF/DCV ± RBV	0 (0)	122 (10.0)	
ELB/GRZ	2 (14.3)	155 (12.7)	
GLE/PIB	2 (14.3)	191 (15.6)	
SOF/VEL	0 (0)	4 (0.3)	
HCC history, *n* (%)			0.34
No	12 (85.7)	1101 (90.0)	
Yes, non-viable	1 (7.1)	100 (8.2)	
Yes, viable	1 (7.1)	22 (1.8)	

AST: aspartate aminotransferase; ALT: alanine aminotransferase; FIB-4: fibrosis-4 index; HBsAg: hepatitis B surface antigen; PrOD: Paritaprevir/ritonavir/Ombitasvir/Dasabuvir; DCV: Daclatasvir; SOF: Sofosbuvir; LDV: Ledipasvir; ELB: Elbasvir; GRZ: Grazoprevir; VEL: Velpatasvir; GLE: Glecaprevir; PIB: Pibrentasvir; RBV: ribavirin; HCC: hepatocellular carcinoma; SVR: sustained virological response. *All interferon-based therapy

the different DAA regimens on the impact of SVR in patients with HCC remains unclear[32]. It is noteworthy that in some studies, patients may receive possibly inadequate or low-potency treatments such as simeprevir/SOF 12 weeks, SOF/LDV 12 weeks in treatment-experienced patients or SOF/ribavirin regimens. It is interesting as to whether the regimens influence the SVR rate. In the present study, we observed similar SVR rates between patients with and without HCC, or HCC patients with and without active diseases in patients with adherence to potent DAAs. The very high SVR rates (> 98%) might prevent negative impact on the responses. Our study has emphasized the importance of potent DAAs in addition to good compliance in patients with HCC.

It is not clear why the presence or history of HCC might influence the likelihood of achieving SVR. We propose some mechanisms for the suboptimal effects of DAAs in patients with HCC. Firstly, tumor cells serve as a sanctuary site for HCV where the replication of the HCV is preserved[33]. Secondly, HCV within tumor cells might evade the antiviral effects of DAA therapy due to ineffective blood delivery to the target site[34]. Thirdly, poor cancer immunity and altered tumor microenvironment has also been linked to altered antiviral efficacy of DAA therapy[35]. Since the SVR is highly related to the effective distribution of the drug, different vascularity changes in HCC or the treated HCC might also be causative. In our patients, good adherence and sufficient duration and dosage of the DAAs might have possibly overcome the barriers for efficacy by HCC.

There are some limitations in the present study. Firstly, a retrospective observational study design may possess some selection bias in obtaining the real efficacy of the therapy. Secondly, we did not record the real-world withdrawal rate of the HCC patients receiving the DAAs although the treatment duration was shortened and the potency increased by the currently widely used DAAs, which may have improved the rate of complete treatment and discontinuation significantly. Thirdly, with a high cure rate for HCV, we did not observe any impact of the DAA therapy on the natural course of the HCC. The controversies of the influence of HCV therapy by DAAs have been discussed with more evidence from the recent systematic reviews and meta-analyses disputing the unfavorable effects on the development of more advanced recurrence or early recurrence in patients with HCC[35]. Lastly, because of the relatively small number of HCC patients treated by DAAs in our study, the statistical non-significance in HCC and non-HCC patients possibly needs further large-scale studies for validation.

In conclusion, we have demonstrated similar SVR rates in patients with HCC, either active or inactive, receiving a complete course of potent DAAs in Taiwan. With high potent DAAs available and easier and more convenient care including shorter duration and less adverse effects during treatment, our results suggest the importance of adherence to DAA therapy and the preference of treating HCV aggressively for HCC patients in clinical settings in Taiwan.

DECLARATIONS

Authors' contributions

Conceived and planned the experiments: Dai CY, Huang CF, Chuang WL, Yu ML
Performed the analytic calculations: Dai CY, Huang CF, Tsai PC, Lin CC, Yu ML
Contributed to patient and sample preparation: Dai CY, Huang CF, Hsieh MH, Huang CI, Yeh ML, Yang JF, Wei YJ, Hsu CT, Liang PC, Lin YH, Huang JF, Chuang WL, Yu ML
Contributed to the interpretation of the results: Dai CY, Huang CF, Tsai PC, Lin CC, Lee MS, Chuang WL, Yu ML
Took the lead in writing the manuscript: Dai CY, Huang CF, Yu ML
Supervised the project: Yu ML

Availability of data and materials

The data source came from Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital. Data could be released to the public only when approval of the owner.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The institutional review board of the Kaohsiung Medical University Hospital approved the protocols, which followed the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients provided written informed consent. There was no specific ethic consideration during the study.

Consent for publication

Not applicable.

REFERENCES

1. WHO. Global Cancer Observatory. Available from: http://globocan.iarc.fr/old/FactSheets/cancers/liver-new. [Last accessed on 30 Mar 2020]
2. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-80.
3. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, et al.; Global Burden of Disease Liver Cancer Collaboration. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA Oncol 2017;3:1683-91.
4. Yu ML, Huang CF, Yeh ML, Tsai PC, Huang CI, et al. Time-degenerative factors and the risk of hepatocellular carcinoma after antiviral therapy among hepatitis c virus patients: a model for prioritization of treatment. Clin Cancer Res 2017;23:1690-7.
5. Huang CF, Yeh ML, Huang CI, Liang PC, Lin YH, et al. Equal treatment efficacy of direct-acting antivirals in patients with chronic hepatitis C and hepatocellular carcinoma? A prospective cohort study. BMJ Open 2019;9:e026703.
6. Huang CF, Iio E, Jun DW, Ogawa E, Toyoda H, et al. Direct-acting antivirals in East Asian hepatitis C patients: real-world experience from the REAL-C Consortium. Hepatol Int 2019;13:587-98.
7. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2017:S0168-8278(17)32273-0.
8. Huang CF, Yu ML. Direct-acting antivirals response in hepatocellular carcinoma: does the presence of hepatocellular carcinoma matter? Clin Mol Hepatol 2019;25:168-71.
9. Ji F, Yeo YH, Wei MT, Ogawa E, Enomoto M, et al. Sustained virologic response to direct-acting antiviral therapy in patients with chronic hepatitis C and hepatocellular carcinoma: A systematic review and meta-analysis. J Hepatol 2019;71:473-85.
10. Saberi B, Dadabhai AS, Durand CM, Philosophe B, Cameron AM, et al. Challenges in treatment of hepatitis C among patients with hepatocellular carcinoma. Hepatology 2017;66:661-3.
11. AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis 2018;67:1477-92.
12. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018;69:461-511.
13. Omata M, Kanda T, Wei L, Yu ML, Chuang WL, et al. APASL consensus statements and recommendations for hepatitis C prevention, epidemiology, and laboratory testing. Hepatol Int 2016;10:681-701.
14. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317-70.
15. Vermehren J, Yu ML, Monto A, Yao JD, Anderson C, et al. Multi-center evaluation of the Abbott RealTime HCV assay for monitoring patients undergoing antiviral therapy for chronic hepatitis C. J Clin Virol 2011;52:133-7.
16. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol 1991;13:372-4.
17. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-50.
18. Lin YH, Yeh ML, Huang CI, Yang JF, Liang PC, et al. The performance of acoustic radiation force impulse imaging in predicting liver fibrosis in chronic liver diseases. Kaohsiung J Med Sci 2016;32:362-6.
19. Wang CC, Liu CH, Lin CL, Wang PC, Tseng TC, et al. Fibrosis index based on four factors better predicts advanced fibrosis or cirrhosis than aspartate aminotransferase/platelet ratio index in chronic hepatitis C patients. J Formos Med Assoc 2015;114:923-8.
20. Yu ML, Dai CY, Huang JF, Hou NJ, Lee LP, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut 2007;56:553-9.
21. Yu ML, Dai CY, Huang JF, Chiu CF, Yang YH, et al. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. Hepatology 2008;47:1884-93.
22. Dai CY, Yeh ML, Huang JF, Chuang WL, Yu ML. Insurance status and treatment candidacy of patients with hepatitis C: Taiwanese patients are luckier. Hepatology 2011;53:1399.
23. Huang JF, Yu ML, Huang CF, Chiu CF, Dai CY, et al. The efficacy and safety of pegylated interferon plus ribavirin combination therapy in chronic hepatitis c patients with hepatocellular carcinoma post curative therapies - a multicenter prospective trial. J Hepatol 2011;54:219-26.
24. Dai CY, Chen DS, Chen PJ, Kao JH, Liu CJ, et al. National registration database for the first year (2017) national health insurance reimbursed direct antiviral agents therapy for chronic hepatitis C in Taiwan. Hepatology 2018;68:403A.
25. Singal AK, Singh A, Jaganmohan S, Guturu P, Mummadi R, et al. Antiviral therapy reduces risk of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. Clin Gastroenterol Hepatol 2010;8:192-9.
26. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Int Med 2013;158:329-37.
27. Kamp WM, Sellers CM, Stein S, Lim JK, Kim HS. Impact of direct acting antivirals on survival in patients with chronic hepatitis C and hepatocellular carcinoma. Sci Rep 2019;9:17081.
28. Dang H, Yeo YH, Yasuda S, Huang CF, Iio E, et al. Cure with interferon free DAA is associated with increased survival in patients with HCV related HCC from both East and West. 2019; Epub ahead of print. doi: 10.1002/hep.30988.
29. Beste LA, Green PK, Berry K, Kogut MJ, Allison SK, et al. Effectiveness of hepatitis C antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma. J Hepatol 2017;67:32-9.
30. Prenner SB, VanWagner LB, Flamm SL, Salem R, Lewandowski RJ, et al. Hepatocellular carcinoma decreases the chance of successful hepatitis C virus therapy with direct-acting antivirals. J Hepatol 2017;66:1173-81.
31. Radhakrishnan K, Di Bisceglie AM, Reddy KR. Treatment status of hepatocellular carcinoma does not influence rates of sustained

virologic response: an HCV-TARGET analysis. Hepatol Commun 2019;3:1388-99.
32. Ji F, Yeo YH, Wei MT, Wei B, Dang S, et al. Hepatocellular carcinoma decreases the effectiveness of hepatitis C antiviral treatment: Do direct-acting antiviral regimens matter? Hepatology 2018;67:1180-2.
33. Niu J, Kumar U, Monjardino J, Goldin R, Rosin D, et al. Hepatitis C virus replication in hepatocellular carcinoma. J Clin Pathol 1995;48:880-2.
34. Konjeti VR, John BV. Interaction between hepatocellular carcinoma and hepatitis C eradication with direct-acting antiviral therapy. Curr Treat Options Gastroenterol 2018;16:203-14.
35. Sachdeva M, Chawla YK, Arora SK. Immunology of hepatocellular carcinoma. World J Hepatol 2015;7:2080-90.