De-novo versus recurrent hepatocellular carcinoma following direct-acting antiviral therapy for hepatitis C virus

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Introduction A recent appearance of direct-acting antivirals (DAAs) led to a surge in hepatitis C virus (HCV) management. Nowadays, a large proportion of treated patients have cirrhosis with a retained possibility to develop hepatocellular carcinoma (HCC) even after complete cure. We aimed to study tumoral differences between patients who developed HCC after DAAs as either a recurrence or de-novo HCC.

Methods We retrospectively analyzed 89 patients who presented to our HCC multidisciplinary clinic with HCC lesions following DAA therapy. A total of 45 patients had complete response to HCC according to the modified Response Evaluation Criteria in Solid Tumors before DAAs intake. Another 44 patients developed de-novo lesions after DAA treatment. Both groups were compared regarding their baseline characteristics, tumor criteria, response to DAAs as well response to HCC treatment.

Results Both groups showed no significant difference regarding their baseline characteristics (age, sex, Child–Pugh score, and performance status) or response to DAAs ($P = 0.5$). No significant difference was present between groups according to number, site, and size of lesions. However, time elapsed between the end of DAAs therapy and first diagnosis of HCC was significantly longer in de-novo group (15.22 ± 16.39 months) versus recurrence group (6.76 ± 5.1 months) ($P = 0.008$). In addition, response to ablation was significantly better in de-novo lesions compared with recurrent HCC ($P = 0.03$).

Conclusions Although de-novo HCC lesions significantly developed later than recurrent lesions in DAAs-treated patients, their response rates were significantly better. No differences were detected between both groups in their response to DAAs and their tumoral characteristics. Eur J Gastroenterol Hepatol 30:39–43

Introduction

Globally, hepatocellular carcinoma (HCC) is considered a serious malignancy with an estimated prevalence of 5.6%. It is also considered the second most common cause of all cancer-related deaths [1]. Regarding the natural history of hepatitis C virus (HCV) infection, studies reported that in approximately 20–30% of patients with chronic hepatitis C, the liver progresses toward liver cirrhosis [2,3]. When liver cirrhosis is established, the annual rate of liver cancer occurrence is ~3.5% [4,5]. HCV acts to be carcinogenic through several factors, whether through direct viral oncogenic effects or through chronic inflammation and fibrosis associated with chronic viral infection [6].

As a drug exerting both direct antiviral and antitumor effects, pegylated interferon (IFN) was early identified as an ideal drug for preventing HCV replication and HCC development [7,8]. These results were confirmed in many subsequent studies including different treatment regimens and patient populations that reported decreased HCC development after achievement of sustained virological response (SVR), taking in consideration that SVR rate was 50% in patients treated with pegylated IFN and ribavirin [9,10].

IFN-free regimen using new direct-acting antiviral (DAA) drugs achieved a revolution in the treatment of patients with chronic hepatitis C, accomplishing more than 95% SVR rate and allowing to treat compensated and decompensated patients with cirrhosis who were never eligible to be treated by IFN-based regimen [11].

Generally, the rate of HCC incidence strongly declined after SVR but did not abolished, with an incidence of HCC ranging from 0.4 to 2% per year after viral clearance [12]. However, the effect of DAA therapy on HCC occurrence in patients without HCC at baseline or on the tumor recurrence rate after proper ablation of HCC was not studied. Two studies were recently published that reported increased aggressiveness and rates of HCC recurrence in patients who were treated with DAAs after achieving a complete response curative HCC therapy, raising the debate around such a highly confusing issue [13,14].

The aim of this study was to study tumor differences between patients who developed HCC after DAA treatment as either a recurrence after confirmed complete

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ablation (before their management with DAAs) or de-novo appearance of HCC lesions.

Patients and methods

This retrospective study analyzed 89 patients with HCC who attended our HCC multidisciplinary clinic, Kasr Alaini Hospital, Cairo University, Egypt, and were diagnosed by noninvasive criteria according to AASLD guidelines [triphasic computed tomography (CT) and/or contrast enhanced MRI with or without elevated α-fetoprotein] [15] during the period of October 2014 till December 2015. They were primarily managed for HCV using DAA regimens. Forty-four patients developed de-novo lesions after DAAs treatment and are plotted against 45 patients with a history of previous successfully completed HCC ablation (complete response) (according to the modified Response Evaluation Criteria in Solid Tumors guideline) [16] before intake of DAAs who developed HCC recurrence after DAAs intake away from the previously ablated lesion. Both group of patients were compared regarding their baseline characteristics, tumor-related criteria, the length of follow-up until HCC development, the duration between the complete ablation and the start of the DAAs, their response to DAAs therapy for HCV in addition to their response to ablation methods for HCC lesions.

The study population was treated in treatment centers supervised by the National Committee for Control of Viral Hepatitis (NCCVH) and were followed-up according to national guidelines for management of HCV in Egypt, where genotype 4 is the most prevalent. The used DAAs were sofosbuvir-based lines of treatment offered in relation to chronological period to NCCVH guidelines [17]. Patients were subjected to monthly follow-up schedule during treatment duration to confirm safety, and then at weeks 4 and 12 after the end of treatment to confirm SVR.

For HCC lesions that developed after HCV treatment by DAAs, all patients were diagnosed and managed according to international guidelines for HCC [15,18] and the ethics principles of the declaration of Helsinki for GCP guidelines. According to clinical data, laboratory data, and radiological tumor assessment, decisions of management included the following: surgical resection, microwave ablation (MWA), combined MWA and transarterial chemoembolization (TACE), percutaneous ethanol injection, TACE as well as supportive treatment. Performing triphasic CT imaging 4 weeks after treatment and every 3 months during the first year and then the patients returned to their routine surveillance program every 6 months if proved well ablated was the follow-up policy for patients with HCC subjected to treatment method to assess achievement of response.

Tumor response was rated using the modified Response Evaluation Criteria in Solid Tumors guideline [16] and was rated as follows:

(1) Complete response: CT scans with no contrast enhancement inside the lesion in the arterial phase.
(2) Partial response: less than 30% decrease in sum of all target lesions in longest axis measurement.
(3) Progressive disease: more than 20% increase in viable target lesions.
(4) Stable disease: non-PR and non-PD.

Statistical analysis

Regarding statistical analysis, in our study, we represented the numerical data as mean ± SD, whereas the categorical data are reported as numbers and percentages. Student's *t*-test and χ^2-test are used when needed. Statistically significant difference is considered if probability of occurrence by chance is 5% or less ($P < 0.05$).

Results

In our retrospective study, baseline characteristics of patients and the developed tumor at the time of diagnosis are shown in Table 1 according to tumor status as either de-novo or recurrent lesions. Patients with de-novo lesions (group 1) and those with recurrent HCC after DAAs (group 2) matched in the demographic characteristics (age, sex, and performance status, $P = 0.9$, 0.6, and 0.7, respectively), hepatic status (Child–Pugh score, $P = 0.6$), serum α-fetoprotein ($P = 0.2$), and radiological features of evolved tumors (number, site, and size of tumors, $P = 0.9$, 0.2, and 0.39, respectively). However, the follow-up duration until HCC development was significantly longer in de-novo group (15.22 ± 16.39 months) versus recurrence group (6.76 ± 5.1 months) ($P = 0.008$).

For the recurrent HCC group (group 1), we followed the national protocol for HCV treatment proposed by the NCCVH as patients with cirrhosis with previous HCC should have a waiting time of 6 months or more after complete response of their tumor. Regarding those with primary tumor, the median value of the primary tumor size was 4.1 cm, and the applied treatments were curative, including 64.3% who received microwave ablation, 28.5% who received radiofrequency ablation, and 7.2% received hepatectomy.

Regarding the response to HCV management, statistical analysis revealed no differences between both groups in their response rate to DAAs (70.5 vs. 64.4%, $P = 0.5$). Furthermore, substudying of their responses according to the different lines of sofosbuvir-based therapy showed no statistical difference ($P = 0.4$) (Table 2).

The different decisions of HCC management (TACE, MWA, percutaneous ethanol injection, resection, combined TACE and MWA, and supportive treatment) were comparably distributed between the two studied groups without statistical significance ($P = 0.2$). However, response to ablation, either complete (72.7 vs. 42.2%) or incomplete ablation (partial response and stable disease) (17.8 vs. 6.8%), was significantly better in the de-novo lesions as compared with the HCC recurrence ($P = 0.03$) (Table 3).

Discussion

In our study, we retrospectively analyzed 89 patients who presented to our HCC multidisciplinary clinic with HCC lesions after their HCV management using sofosbuvir-based regimens. Recent studies highlighted the increased rates of HCC recurrence in patients who were treated with DAAs and achieved a complete response to the used ablative method [13, 14]. There have been different studies that analyzed the possible mechanisms for development of HCC lesions in patients who received sofosbuvir-based regimens. Viral-induced inflammation and microenvironment alteration were accused of chronic liver insult and initiation of the tumor. On the

Table 1 . Baseline characteristics of the studied patients

Items	HCC recurrence ($N=45$)	HCC *de novo* ($N=44$)	*P* value
Age (mean ± SD) (years)	57.76 ± 6.516	58.00 ± 6.847	0.9
Males [*n* (%)]	35 (77.8)	36 (81.8)	0.6
Child–Pugh, A/B [*n* (%)]	35 (77.8)/10 (22.2)	36 (81.8)/8 (18.2)	0.6
Performance status [*n* (%)]			
0	28 (62.2)	28 (63.6)	0.7
1	13 (28.9)	14 (31.8)	
2	3 (6.7)	2 (4.5)	
3	1 (2.2)	0 (0.0)	
ALT (mean ± SD) (IU/l)	43.37 ± 29.391	62.21 ± 38.286	0.01
AST (mean ± SD) (IU/l)	56.43 ± 34.564	68.10 ± 39.354	0.1
Albumin (mean ± SD) (g/dl)	3.586 ± 0.6858	3.549 ± 0.5565	0.8
Bilirubin (mean ± SD) (mg/dl)	1.655 ± 2.6319	1.318 ± 0.9343	0.4
INR (mean ± SD)	1.171 ± 0.18643	1.21 ± 0.17066	0.02877
Hemoglobin (mean ± SD) (g/dl)	12.8317 ± 1.53825	13.0837 ± 1.84519	0.5
Platelet count (mean ± SD) ($\times 10^9$/l)	125.19 ± 54.448	132.91 ± 61.617	0.5
AFP [median (range)] (ng/ml)	510 000 (2.5–60 500)	305 600 (1.89–4686)	0.2
Number of lesions [*n* (%)]			
Single	30 (66.7)	30 (68.2)	0.9
Two	4 (8.9)	5 (11.4)	
Multiple	11 (24.4)	9 (20.5)	
Site of lesions [*n* (%)]			
Right lobe	28 (62.2)	34 (77.3)	0.2
Left lobe	10 (22.2)	7 (15.9)	
Bilateral	7 (15.6)	3 (6.8)	
HCC size (mean ± SD) (cm)	4.707 ± 2.5845	3.695 ± 2.3019	0.3941

AFP, α-fetoprotein; HCC, hepatocellular carcinoma; INR, international normalized ratio.

Table 2. Response to different direct-acting antivirals combination

Item	HCC recurrence ($N=45$)	HCC *de novo* ($N=44$)	*P* value
Response to DAAs [*n* (%)]			
Responder	29 (64.4)	31 (70.5)	0.5
Nonresponder	4 (8.9)	4 (9.1)	
Relapsers	12 (26.7)	7 (15.9)	
DAA combination [*n* (%)]			
SOF + RIB + IFN	8 (17.8)	3 (6.8)	
SOF + RIB	19 (42.2)	16 (36.4)	
SOF + SIM	9 (20.0)	11 (25.0)	
SOF + DAC	5 (11.1)	8 (18.2)	0.4
SOF + DAC + RIB	4 (8.9)	6 (13.6)	

DAC, daclatasvir; HCC, hepatocellular carcinoma; INF, interferon; RIB, ribavirin; SIM, semiprevir; SOF, sofosbuvir.

Table 3. Different lines of hepatocellular carcinoma management

Items	HCC recurrence ($N=45$)	HCC *de novo* ($N=44$)	*P* value
Time to detection of HCC (mean ± SD) (months)	6.76 ± 5.1	14 ± 16.02	0.008
Treatment method for HCC [*n* (%)]			
TACE	23 (51.1)	19 (43.2)	
MWA	4 (8.9)	11 (25)	
PEI	0	1 (2.3)	
Resection	2 (4.4)	0	0.2
TACE + MWA	1 (2.2)	1 (2.3)	
Supportive	15 (33.3)	12 (27.3)	
Response to HCC treatment [*n* (%)]			
Complete	15 (33.3)	27 (61.4)	0.02
Partial	8 (17.8)	3 (6.8)	
No response	22 (48.9)	14 (31.8)	

HCC, hepatocellular carcinoma; MWA, microwave ablation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization.

contrary, the immune system plays an antitumor role [18–21]. Other studies highlighted the DAA treatment-induced modification of IFN response gene expression and natural killer cells [22,24]. Another hypothesis took in consideration the antitumor response dysregulation after the DAA-induced sudden decrease of HCV viral load which promotes tumor recurrence [25].

Reig *et al.* [13] called for attention toward the unexpected high rate of HCC recurrence after DAA therapy in patients with prior HCC. They reported 27.6% radiologic tumor recurrence after a median follow-up of 5.7 months with pattern of recurrence varying from intrahepatic growth, to newly developed intrahepatic lesions, to infiltrative ill-defined HCC and/or extrahepatic lesions. A large debate developed between studies that reported similar cautions and other trials, studies, and letters to the editor that totally opposed the Reig and colleagues report [26–32].

In our study, the follow-up duration of DAAs therapy until HCC development in recurrence group was 6.76 ± 5.1 months, which was consistent with the follow-up duration reported by Reig and colleagues (5.7 months) from the initiation of the DAA treatment. However, this duration was significantly longer in our de-novo group (15.22 ± 16.39 months). In the ANRS studies, they reported an incidence of 18/1000 person/year during the first 6 months after DAA therapy; this incidence dropped by half after 12 months [28]. These results support the theory of downregulation of the antitumor response of the immune system with the brutal DAAs-induced HCV clearance, as boosting the growth of invisible HCC because of the attenuation of immune surveillance shall take significantly shorter duration in patients with previous history of ablated HCC lesions. Moreover, this may partially explain the better prognosis of de-novo lesions that developed later in relation to the time interval to date of DAA therapy, with a possible faster and aggressive tumor growth for tumors that are close to DAA therapy period, whereas late lesions are more in relation to natural course of cirrhosis that can develop to HCC.

We found no significant difference between both groups regarding their baseline characteristics (age, sex, Child–Pugh

score, and performance status) and tumor factors (number, site, and size of lesions). Importantly, response to ablation was significantly better in de-novo lesions compared with HCC recurrence. Conti *et al.* [14] detected 28.85% HCC recurrence in patients with previous HCC (17/59) and 3.16% HCC occurrence in patients without previous HCC (9/285). They reported that Child–Pugh class B, higher liver fibrosis scores, lower platelet count, and history of previous HCC were significantly associated with HCC development using univariate analysis. In addition, multivariate analysis concluded that advanced Child–Pugh score and history of HCC were independently associated with HCC development.

In this study by Conti *et al.* [14], subanalysis of the 59 patients with previous history of HCC founded that younger age and more severe liver fibrosis were significantly associated with HCC recurrence. This may be explained by the deficient immune surveillance (owing to the rapid and abrupt DAAs-induced HCV clearance) that could lead to more advanced liver fibrosis. Regarding response to DAAs, even after subanalysis according to the different lines of sofosbuvir-based therapy, there were no detected differences between the studied groups and no correlations were found between the used DAAs regiment and HCC recurrence or de-novo occurrence, confirming what was reported by Conti *et al.* [14].

Our study revealed a relatively low response in HCC recurrence group. Actually, we cannot definitely assume or comment on low SVR rates in our studied populations as more than 50% were treated by one DAA only (sofosbuvir/ribavirin or sofosbuvir/IFN/ribavirin) and carried low SVR rates in patients with cirrhosis. So, mostly it is a factor of suboptimal line of treatment in a respectable difficult-to-treat group of patients (patients with cirrhosis who were either well compensated or early decompensated). In a recent study by Prenner *et al.* [33], the presence of active HCC tumor at the time of start of antiviral therapy was the greatest independent predictor of treatment failure. These patients with active HCC at the time of DAA initiation had eight-folds increased risk of failing HCV therapy compared with those without HCC, whereas patients who received DAA therapy after complete ablation or after removal of their tumor resulted in excellent SVR rates, similar to those without HCC. When they studied the failure rates across treatment regimens, patients who failed DAA treatment were more likely to have received an inadequate regimen. When they performed multivariate analysis, inadequate regimens were predictive of treatment failure [33].

So, we concluded that de-novo HCC lesions significantly developed later than recurrent lesions in patients treated for HCV using sofosbuvir-based therapy and their response rates were significantly better. No differences were detected between both groups in their response to DAAs as well as their tumor characteristics. This study still poses the question of proper timing to treat patients with HCV who had ablated HCC lesions and the need to modify their surveillance programs to shorter time intervals to detect HCC lesions.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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