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Research Article

Changing Patterns of Hepatocellular Carcinoma after Treatment with Direct Antiviral Agents

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Hepatocellular carcinoma · Direct antiviral agents · HCC pattern · Hepatitis C virus

Abstract
Introduction: The impact of direct antiviral agents (DAAs) on the development of hepatocellular carcinoma (HCC) is controversial. One important aspect of this controversy is the changing pattern of HCC. ***Objective:*** In this study, we attempted to assess the changes in the pattern of HCC after treatment with DAAs. ***Methods:*** A total of 51 HCC patients after DAA treatment and 54 HCC patients without DAA treatment were included. The diagnosis of HCC was based on typical dynamic CT and/or MRI criteria in both groups. Liver status was assessed by means of the fibrosis 4 index (Fib-4), Child-Pugh classification, and model for end-stage liver disease (MELD). HCC infiltrative pattern, portal vein thrombosis (PVT), local and distant metastases, and α-fetoprotein (AFP) level were compared in the 2 groups. The staging of HCC and treatment decisions were made in both groups following the Milan criteria, Barcelona Clinic Liver Cancer staging, tumor-node-metastasis staging, and Cancer of the Liver Italian Program categorization. ***Results:*** The mean age of the HCC patients after DAA treatment (59.1± 7.4 years) was older than that of the HCC patients without DAA treatment. There was no significant difference between groups regarding sex distribution. The mean Fib-4 score (4.84 ± 3.53) was significantly lower in HCC patients after DAA treatment than in those without DAA treatment. The frequency of the infiltrative HCC pattern, PVT, and regional lymph node metastasis was significantly higher in HCC patients after DAA treatment than in those without DAA treatment

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($p \leq 0.05$); mean AFP level (5,085.2 ± 11,883.2 ng/mL) was also significantly higher. HCC patients after DAA treatment had significantly advanced stages and limited treatment options ($p \leq 0.05$). ***Conclusion:*** The changing HCC pattern after DAA treatment may suggest the need for new HCC staging and treatment protocols.

Introduction

Hepatocellular carcinoma (HCC) is the second-most common and fastest rising cause of cancer-related death [1]. In Egypt, HCC constitutes a significant public health problem. HCC is responsible for 33.63 and 13.54% of all cancers in Egyptian males and females, respectively [2]. Chronic hepatitis C virus (HCV) infection is a leading cause of HCC. The overall prevalence of HCV among Egyptian HCC cases is nearly 84% [3].

The eradication of HCV with direct antiviral agents (DAAs) with cure rates of >90% has been a major breakthrough in the management of patients with chronic hepatitis C. However, the HCC risk has not been eliminated, especially in patients with advanced fibrosis [4, 5].

The impact of DAAs on the development of HCC is controversial. Although some [6–8] authors have suggested the presence of a link between DAAs and the development of HCC, others have reported the absence of a link [9–12]. This controversy can be divided into 3 fundamental aspects: the impact of DAAs on the incidence rate of HCC, the temporal association between the initiation of DAA treatment and the development of HCC, and finally, the aggressive pattern of HCC [13].

The aggressive pattern of HCC after DAA treatment has been previously reported. It has been reported that HCC after DAA treatment is associated with advanced Barcelona Clinic Liver Cancer (BCLC) stage [6] and early vascular invasion [7]. Notably, this aggressiveness of HCC after DAA treatment has a negative impact on survival and response to ablation therapy [8]. We have attempted to assess changes in the pattern of HCC after DAA treatment and the impact of this on HCC treatment decisions.

Materials and Methods

This report describes a single-center, case-controlled prospective study that was performed between December 2014 and June 2019 at the Gastroenterology and Hepatology Unit, Department of Internal Medicine, El Hussein University Hospital, Cairo, Egypt. We included all patients with HCV-related HCC who presented to our unit in that period, i.e., HCC patients after DAA treatment (n = 51) and HCC patients without DAA treatment (n = 54). Patients with concomitant autoimmune hepatitis and metabolic liver disease as well as those coinfected with hepatitis B virus (HBV) and/or human immune deficiency virus (HIV) were excluded.

Patient Assessment before DAA Treatment

The diagnosis of HCV infection was confirmed by the quantitative assessment of HCV RNA in HCC patients after DAA treatment (n = 51). The eligibility for DAA treatment followed the National Committee for Control of Viral Hepatitis guidelines, as previously mentioned [14]. A history of HCV relapse, the type of DAA regimens received, the time between the beginning and end of the DAA regimens, and the HCC diagnosis were assessed. In addition, the α-fetoprotein (AFP) level was directly assessed before the last DAA regimen. Sustained virological response 12 (SVR12) during HCV treatment and treatment failure were assessed and defined as previously mentioned [14].

HCC Diagnosis and Pattern Evaluation

The diagnosis of HCC was based on typical dynamic CT and/or MRI criteria [15]. The pattern of HCC was assessed in all patients (n = 105). This included the largest tumor size, infiltrative patterns on imaging, HCC

multiplicity, distant and lymph node metastases, malignant portal vein thrombosis (PVT), and elevated AFP. The diagnosis of malignant PVT was based on the presence of 2 of the following factors: a distance from the tumor to the PVT of <2 cm, an HCC size >5 cm, and arterial PVT enhancement [16]. A complete response to HCC treatment was confirmed by dynamic imaging [17] at least 6 months before starting the last DAA regimen.

Patient Assessment at HCC Diagnosis

Age; sex; presenting symptoms; the presence of diabetes mellitus; white blood cell and platelet counts; levels of hemoglobin, serum creatinine, alanine aminotransferase, aspartate aminotransferase (AST), serum albumin, and serum bilirubin; and the international normalized ratio (INR) were assessed at the time of HCC diagnosis in both groups (n = 105).

The diagnosis of liver cirrhosis was assessed at the time of HCC diagnosis. This diagnosis was confirmed by liver biopsy or a combination of clinical, biochemical, and radiological findings [18]. The severity of liver cirrhosis was assessed with the Child-Pugh classification [19] and model for end-stage liver disease (MELD) [20] at the time of HCC diagnosis in both groups.

HCC Staging

The Milan criteria [21], BCLC staging, [22], tumor-node-metastasis (TNM) staging [23], and Cancer of the Liver Italian Program (CLIP) categorization [24] were assessed in both groups (n = 105).

Treatment Decision

The treatment decision for all 105 HCC patients was made by consensus in the local multidisciplinary HCC team. In general, surgical resection was the primary treatment chosen for patients with HCC in the absence of cirrhosis and those with unifocal tumors in the setting of compensated cirrhosis and in the absence of portal hypertension [15]. Living-donor liver transplantation was the primary treatment chosen for patients with decompensated cirrhosis based on the Milan criteria, defined as 1 tumor <5 cm or 3 tumors <3 cm each, without vascular invasion or extrahepatic disease [21]. Radiofrequency ablation (RFA) was the first treatment option for patients with an HCC ≤3 cm and compensated liver cirrhosis, who were not suitable for resection or transplantation. Transarterial chemoembolization (TACE) was recommended for intermediate-stage (BCLC stage B) HCC patients [15]. Sorafenib was recommended for advanced-HCC patients. The best supportive care was recommended for HCC patients with a poor performance status, Child C cirrhosis, and BCLC stage D.

Follow-Up Protocol after HCC Treatment

The initial response evaluation was carried on at 4 weeks for all patients (n = 105). Follow-up of patients who underwent liver resection or RFA consisted of clinical and laboratory evaluations for liver decompensation monthly, and early detection of HCC recurrence by dynamic CT or MRI every 3 months for the first 2 years and surveillance every 6 months after that [25]. In cases of tumor recurrence, reassessment of the patient was performed, and retreatment was planned accordingly. Following TACE, further follow-up consisted of clinical and laboratory evaluations for liver decompensation monthly and dynamic CT or MRI for tumor progression every 3 months to guide therapy decisions. For patients taking sorafenib, the clinical and laboratory evaluations were performed every 2 months. Clinical and laboratory evaluations were performed monthly for patients on the best supportive care. The AFP level was measured every 3 months for patients with a high level at HCC diagnosis.

Statistical Analysis

Continuous variables were expressed as the mean and standard deviation (SD). Categorical variables were presented as frequency and percentage. Comparisons between groups were made by using the Student t test for continuous variables and the χ^2 or Fisher exact probability test for categorical data. The two-tailed, paired Student t test was used to test for the significance of differences between baseline and posttreatment variables. A p value of ≤0.05 was considered statistically significant. Data were analyzed using SPSS v19.0 for Windows (SPSS, Chicago, IL, USA).

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Table 1. Characteristics of HCC patients after treatment with DAAs

Treatment-experienced patients	9 (17.6)
Treatment-naïve patients	42 (82.4)
Level of AFP before the last DAA, ng/mL	56.3±124.1
Response to DAA	
A sustained virological response	49 (96)
No response	2 (4)
Antiviral drug administered	
Sofosbuvir	51 (100)
Daclatasvir	41 (80.39)
Ribavirin	34 (66.6)
Pegylated interferon	8 (15.6)
Simeprevir	3 (5.8)
Time from start of DAA to HCC diagnosis, months	15.8±14.6

Values express *n* (%) or mean ± SD. HCC, hepatocellular carcinoma; DAAs, direct antiviral agents; AFP, α-fetoprotein.

Results

Patients' Characteristics before DAA Treatment

Nine of the 51 patients (17.6%) had previous experience with HCV treatment; 3 of them reported HCV relapse after pegylated interferon and ribavirin (PEG-INF/RBV) dual therapy and 6 after sofosbuvir (SOF)-based therapy. All 51 patients received SOF-based treatment in the last DAA regimen before HCC diagnosis. The mean AFP level just before starting the last DAA regimen was elevated (56.3 ± 124.1 ng/mL). The rates of SVR and treatment failure were 96 and 4%, respectively. The mean time between the start of the last DAA regimen and HCC diagnosis was 15.8 ± 14.6 months (Table 1).

Patients' Characteristics at HCC Diagnosis

The mean age of the HCC patients after DAA treatment (59.1 ± 7.4 years) was older than that of the HCC patients without DAA treatment (56.3 ± 7.3 years) at the time of HCC diagnosis. There were 42 (82.4%) male and 9 (17.6%) female HCC patients after DAA treatment. No significant difference was found between the groups regarding sex distribution (Table 2). Six (11.8%) HCC patients after DAA treatment had a history of HCC cure, but at least 6 months before the last DAA regimen, 45 (88.2%) developed de novo HCC. More HCC patients after DAA treatment than HCC patients without DAA treatment were symptomatic. Indeed, the rate of accidentally discovered HCC was lower in patients after DAA treatment (17.6%) than in HCC patients without DAA treatment (29.6%). The mean fibrosis 4 index (Fib-4) score (4.84 ± 3.53) was significantly lower in HCC patients with DAA treatment than in those without DAA treatment ($p \leq 0.05$). Of the 51 HCC patients with DAA treatment, 5 (8.9%) had no indication of liver cirrhosis. In contrast, all 54 HCC patients without DAA treatment had liver cirrhosis. The frequency of Child class A cirrhosis was 52.17 and 44.6% in the HCC patients with and without DAA treatment, respectively. The frequency of HCC patients after DAA treatment with decompensated cirrhosis (Child class B/C) was 47.83%. In contrast, the majority (55.6%) of HCC patients without DAA treatment had decompensated cirrhosis (Child class B/C). The mean MELD score in HCC patients with and without DAA treatment was 11.6 ± 5.2 and 12.2 ± 5.3, respectively (Table 2).

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Table 2. Patient characteristics at the time of diagnosis of HCC

	HCC after DAAs (n = 51)	HCC without DAAs (n = 54)	t	χ^2	F	p
Age, years	59.1±7.4	56.3±7.3			3.7	0.05
Male	42 (82.4)	43 (79.6)		0.12		0.72
Female	9 (17.6)	11 (20.4)				
Presenting symptom				14.10		0.02
Abdominal pain	32 (62.7)	19 (35.2)				
Accidental	9 (17.6)	16 (29.6)				
Ascites	4 (7.8)	10 (18.5)				
Lower limb edema	1 (2)	2 (3.7)				
Jaundice	3 (5.9)	3 (5.6)				
Fatigue	2 (3.9)	0 (0)				
Others	0 (0)	4 (7.4)				
Diabetes mellitus				21.05		0.58
Yes	13 (25.5)	16 (29.6)				
No	38 (74.5)	38 (70.4)				
Hemoglobin	11.8±1.8	11.2±1.9			3.079	0.08
White blood cell count	7.3±6.4	6.2±2.7			1.546	0.21
Platelets	150.5±108.5	128.4±67.9			1.590	0.21
Serum creatinine	0.9±0.4	1.1±0.9			1.181	0.28
Liver status						
ALT	51.5±53.9	61.9±59.4			0.876	0.35
AST	59±53	84.4±86.9			3.238	0.07
Serum albumin	3.3±0.6	3.1±0.8			3.589	0.05
Serum bilirubin	2.5±3.4	1.9±1.5			1.116	0.29
INR	1.3±0.3	1.3±0.3			0.549	0.46
Fibrosis 4 index (range)	4.84±3.53 (1.06–13.33)	6.53±4.78 (1.58–24.92)			4.32	0.042
Fibrosis 4 index				6.16		0.046
<1.45	5 (8.9)	0 (0)				
1.45–3.25	17 (33.3)	16 (29.6)				
>3.25	29 (56.9)	38 (70.4)				
MELD score	11.6±5.2	12.2±5.3	0.23			0.63
Recurrent HCC	6 (11.8)	–	–	–	–	–
De novo HCC	45 (88.2)	–	–	–	–	–

Values are expressed as n (%) or mean ± SD. HCC, hepatocellular carcinoma; DAAs, direct antiviral agents; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model of end-stage liver disease.

HCC Tumor Characteristics after DAA Treatment

At first presentation, HCC tumors after DAA treatment demonstrated aggressive behavior compared with HCC tumors not subjected to DAA treatment. Indeed, the frequency of infiltrative HCC pattern, PVT, and regional lymph node metastasis was significantly higher among HCC patients after DAA treatment than among those without DAA treatment ($p \leq 0.05$). The mean AFP level (5,085.2 ± 11,883.2 ng/mL) was significantly higher among HCC patients after DAA treatment than among those without DAA treatment (Table 3).

Table 3. Aggressive pattern of HCC after treatment with DAAs

	HCC after DAA treatment (n = 51)	HCC without DAA treatment (n = 54)	F	χ^2	p
Portal vein thrombosis				4.22	0.04
Yes	23 (45.1)	14 (25.9)			
No	28 (54.9)	40 (74.1)			
Lymph node metastasis				7.41	0.00
Yes	14 (27.5)	4 (7.4)			
No	37 (72.5)	50 (92.6)			
Distant metastasis				0.92	0.33
Yes	1 (2)	3 (5.6)			
No	50 (98)	51 (94.4)			
Imaging morphology				24.49	0.00
Nodular	30 (58.8)	53 (98.1)			
Infiltrative	21 (41.2)	1 (1.9)			
Number of focal lesions				2.07	0.15
Single	25 (49)	34 (63)			
Multiple	26 (51)	20 (37)			
Size of largest focal lesion, cm	5.4±2.7	5.2±3.2	0.23		0.63
AFP at diagnosis, ng/mL (mean ± SD)	5,085.2±11,883.2	1,492.2±5,121.9	4.12		0.05

Values express n (%), unless otherwise indicated. HCC, hepatocellular carcinoma; AFP, α-fetoprotein; DAAs, direct antiviral agents.

HCC Staging and Treatment Options after DAA Treatment

The vast majority of patients (76.5%) with HCC after DAA treatment were not suitable for liver transplantation based on the Milan criteria; on the other hand, 51.9% of HCC patients without DAA treatment were candidates for liver transplantation ($p < 0.5$). Additionally, the best supportive treatment was the only valid treatment option for 62.8% of the patients with HCC after DAA treatment. There were significant differences between HCC patients after DAA treatment and those without DAA treatment regarding the Milan criteria, BCLC staging, TNM staging, and CLIP categorization ($p < 0.5$) (Table 4).

Discussion

Few reports have commented on the pattern of HCC after DAA treatment [8]. Our study revealed some key findings regarding the pattern of HCC after DAA therapy. We demonstrated that HCC may occur in less-advanced liver disease after DAA treatment. A total of 70% of patients with HCC after DAA treatment had elevated AFP levels before the last DAA induction. An infiltrative HCC pattern and multiple nodules at presentation were significantly more frequent among HCC patients after DAA treatment than among HCC patients without DAA treatment. Advanced HCC stages and the limited number of treatment options are real problems in terms of treatment decisions for HCC patients after DAA treatment. Finally, according to our results, HCC is still detected up to 4 years after starting DAA therapy.

The rate of HCC in HCV patients without antiviral treatment is directly related to the stage of liver fibrosis and cirrhosis. Five years after liver biopsy, only 1% of people with no/mild, moderate, or advanced fibrosis develop HCC, but this figure increases dramatically to 13.4% in patients with cirrhosis [26]. Unexpectedly, the mean Fib-4 score was significantly lower

Table 4. Limited therapeutic options for HCC patients after treatment with DAAs

	HCC after DAA treatment (*n* = 51)	HCC without DAA treatment (*n* = 54)	χ^2	*p*
MILAN criteria			8.92	0.00
Within MILAN	12 (23.5)	28(51.9)		
Beyond MILAN	39 (76.5)	26 (48.1)		
BCLC stage			12.77	0.01
0	3 (5.9)	4 (7.4)		
A	9 (17.6)	16 (29.6)		
B	7 (13.7)	13 (24.1)		
C	21 (41.2)	6 (11.1)		
D	11 (21.6)	15 (27.8)		
TNM classification			22.75	0.00
I	9 (17.6)	26 (48.1)		
II	7 (13.7)	9 (16.7)		
IIIA	10 (19.6)	5 (9.3)		
IIIB	12 (23.5)	5 (9.3)		
IIIC	0 (0)	2 (3.7)		
IVA	13 (25.5)	4 (7.4)		
IVB	0 (0)	3 (5.6)		
CLIP category			21.60	0.00
0	6 (11.8)	11 (20.4)		
1	14 (27.5)	13 (24.1)		
2	5 (9.8)	12 (22.2)		
3	7 (13.7)	16 (29.6)		
4–6	19 (37.3)	2 (3.7)		

Values express *n* (%). HCC, hepatocellular carcinoma; DAA, direct antiviral agent; BCLC, Barcelona Clinic Liver Cancer; TNM, tumor-node-metastasis; CLIP, Cancer of the Liver Italian Program.

among HCC patients after DAA treatment than among those without antiviral treatment. Indeed, the risk of HCC after DAA treatment in patients without cirrhosis has been reported. In addition, the risk is high enough to recommend HCC surveillance in patients with ongoing alcohol use and high Fib-4/APRI (AST-to-platelet ratio index) scores [27]. Notably, 9% of HCC patients after DAA treatment had a Fib-4 score of <1.45, according to our results. Moreover, patients with HCC after DAA treatment had a higher instance of compensated liver disease (57%) and a lower mean MELD score than the HCC patients without antiviral treatment. These results suggest that HCC after DAA treatment may occur in patients with early stages of chronic liver disease, indicating a role for DAA treatment in HCC carcinogenesis among HCV patients. Moreover, these results support the screening of HCV patients for HCC after DAA treatment, even in noncirrhotic patients.

The aggressive behavior of HCC after DAA treatment has been previously reported. Cases of multifocal and infiltrative HCC were reported in 33 and 54% of patients with SVR and HCV relapse after DAA treatment, respectively [28]. Malignant portal vein invasion and local spread through malignant lymphadenopathy were found to be significantly higher among HCC patients after DAA treatment [8]. In line with this, the multifocal and infiltrative HCC patterns were significantly more frequent among our HCC patients after DAA treatment. In general, the AFP level is suggested to be closely related to HCC malignancy and may reflect the aggressiveness of HCC [29–32]. Poor differentiation and an HCC size ≥10 cm are inde-

pendent predictors of elevated AFP level [32–35]. Similarly, multinodular HCC [31, 34] and vascular invasion [31, 36–38] as well as advanced stages of BCLC are correlated with an elevated AFP level [32]. An elevated serum AFP level before DAA therapy has been recognized as one of the common risk factors for HCC [39–41]. It has also been reported as a risk factor for HCC in HCV-infected patients with or without attaining SVR following interferon therapy [39–41]. In agreement with our results, Abdelaziz et al. [8] reported that the mean AFP level was significantly elevated in HCC patients after DAA treatment when compared with HCC patients without DAA treatment. These data indicate the aggressiveness of HCC after DAA treatment and suggest that elevated baseline AFP is a predictor of HCC development after DAA treatment. In addition, patients with an increased AFP level at the end of treatment should be carefully monitored for HCC development or recurrence [42].

The best supportive treatment is the only available management option for 30% of HCC patients after DAA treatment, significantly higher than for HCC patients without DAA treatment (15.5%) [8]. Supportive treatment was chosen for 60% of our HCC patients after DAA treatment and 50% of those without DAA treatment. Likewise, 25% of patients with HCC recurrence after DAA treatment have a deteriorated BCLC classification and are not fit for any intervention [6]. These data may indicate the changing pattern of HCC after DAA treatment and suggest the need to change treatment options and recommendations in HCC after DAA treatment.

It is unclear if HCC risk declines over time after HCV eradication. Recently, it was reported that there was no indication of a downtrend in HCC risk, at least during the first 3.6 years after DAA treatment. These results are in contrast with data on 139 patients with HCV-related cirrhosis who were followed for an average of 15 months and demonstrated a sharp decline in HCC risk in the second year of follow-up [43]. In fact, HCC was detected in our cohort up to 4 years after starting DAA treatment. Ioannou et al. [44] concluded that patients with cirrhosis before achieving SVR after treatment for HCV infection continued to have a high risk of developing HCC (>2%/year) for many years, even if their Fib-4 score decreased; continued surveillance should therefore be implemented for these patients. Patients without cirrhosis but with a Fib-4 score ≥3.25 had a high enough risk to merit HCC surveillance, especially if the Fib-4 score remained ≥3.25 post-SVR. Based on these findings, prolonged HCC surveillance is warranted in HCV patients after DAA therapy.

The prospective nature of our study and the long-term follow-up are strong aspects. The limitation of this study is related to the small number of patients.

Collectively, our study demonstrated the changing pattern of HCC after DAA treatment. Indeed, HCC after DAA treatment seemed to be highly aggressive. In the face of changing HCC patterns, available HCC treatment options and recommendations should be revised. Finally, our results justified the need for prolonged HCC surveillance after DAA therapy.

Statement of Ethics

The study was in compliance with the ethics principles of the Al-Azhar University Faculty of Medicine Research Ethics Committee according to the 1975 Declaration of Helsinki. Informed consent for inclusion in the study was received from all patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Mohamed El Fayoumie and Ashraf Elbahrawy designed the work; Mohamed El Fayoumie, Mahmoud Abdelhady, Ahmed Gawish, Ismail Abdelkhalek, Mohamed Abdelraheem, Alaa Alsawak, and Usama Hantour collected the data and provided technical assistance and discussion; Mohamed El Fayoumie , Ahmed Gawish, Ismail Abdelkhalek, Mohamed Abdelraheem, and Alaa Alsawak performed the locoregional management; Mahmoud Abdelhady performed the surgical management; Ashraf Elbahrawy and Ahmed Alwassief wrote and revised the manuscript; and Ashraf Elbahrawy supervised the work.

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