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Case Report **Open Access**

Hepatocellular carcinoma following direct anti-viral for hepatitis C treatment: a report of an Egyptian case series

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ABSTRACT

Egypt had been vexed by the highest load of chronic hepatitis C in the world. It represents a vast market of the new direct-acting anti-viral drugs (DAAs); effectively treating chronic hepatitis C virus (HCV) infection. Eradication of HCV in Egypt has been challenged by the observed increased diagnosis of hepatocellular carcinoma (HCC) in relation to DAAs therapy. This is the first Egyptian report annotating to a series of sixteen chronic HCV infected cases without a diagnosis of HCC before DAAs therapy and unexpected development of HCC during or after completion of DAAs therapy.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most dreadful sequels of hepatitis C virus (HCV)-related cirrhosis.[1] New direct-acting antivirals (DAA) had successfully created a new era of HCV elimination.[2] However, their role in moderating the incidence of HCC in those patients is still questionable. Beyond the several observations of the proximity between DAAs therapy, and emerging HCC, many systematic reports have been sequentially reported.[3-5] The first one is from Barcelona reported that HCC recurrence in 27.6% of the studied patients after a median follow-up of 5.7 months. Notably, they achieved viral eradication and had no pretreatment evidence of residual HCC.[3] In the Italian cohort that included 59 patients with earlier HCC and 295 patients negative for HCC, the HCC recurred at a rate of 28.8%, while *de novo* HCC showed a lower rate (3.16%).[4] The French report that included 3 studies and 6,000 patients who received interferon (IFN)-free regimens had refuted the Spanish and Italian data. The researchers found no increased

risk of developing *de novo* HCC and a relatively low risk for HCC recurrence.[5]

Amelioration of HCV natural history is the anticipated post treatment target. Sustained virological responses (SVR) and their link to lessened HCV-related morbidity and mortality, including HCC had been interrogated since the era of IFN-containing regimens.[6] This conception has been already recalled in the new era of DAAs with evolving comparable perspectives.[7] This is the first report from Egypt; registering 16 primary HCC cases respective to DAAs therapy.

CASE REPORT

This report includes a series of 16 patients who were diagnosed as Child A HCV-related cirrhosis. They presented to National Liver Institute Hospital, Menofia University, Egypt, to receive care and management as inpatients in the Clinical Hepato-Gastroenterology Department.

The patients were males except for 1 female and at their late fifties. They were diagnosed as having HCV infection during the least 4 years. Pre DAAs treatment evaluation, laboratory, endoscopic as well as tedious professional abdominal imaging [either abdominal ultrasound or computerized tomography (CT) scan] were available for all patients.

All patients received IFN-free, sofosbuvir-based regimens. Sofosbuvir plus ribavirin was prescribed to 11 cases (68.8%), sofosbuvir/daclatasvir plus ribavirin were given to 3 patients (18.8%), 1 patient was given sofosbuvir plus daclatasvir (6.2%), and 1 patient (6.2%) had received sofosbuvir plus simeprevir. SVR at week 12 post treatment was achieved in 13 cases (81.25%).

The patients had completed their treatment regimens, except 2 cases that developed drug-related complications, and stopped the treatment. Only 1 relapse was reported in this study group.

The newer sonography and CT imaging in 2 cases as well as the remaining 14 patients had surprisingly unveiled presence of predominantly small HCC. The small-sized lesions added to the mean timing for HCC detection (4.19 ± 3.48 months post-treatment), and the pre-treatment compensated liver disease have suggested HCC occurrence rather than a continuation of pre-treatment lesions.

Most of these new lesions were small; less than 3 cm in 12 patients (81%), 3-5 cm in 3 cases (18.8%), while 1 patient who was diagnosed with a lesion more than 5 cm. All these patients presented less than 1 year post-treatment (4.19 ± 3.48 months). The focal lesions were mainly cited in the right hepatic lobe (62.5%), 12.5% in the left lobe while multi-focal lesions were detected in 4 cases (25%) [Table 1].

Malignant portal vein thrombosis was radiologically documented in 1 patient (6.25%). Significant biochemical derangements were reported following revelation of HCC. They were significant enough to transfer most of the affected patients from Child class A to Child C cirrhosis [Table 2].

Statistical analysis

Statistical analysis was carried out using SPSS (Statistical Package for Social Science) program. Data was entered as numerical or categorical, as appropriate. Quantitative data was shown as mean, and SD, while qualitative data has been expressed as frequency and percent.

DISCUSSION

Obviously, sofosbuvir is the principal DAA in the current case series and all published reports of HCC connected to DAAs.[8] However, the alleged link between DAAs in general, sofosbuvir or sofosbuvir related metabolites and carcinogenesis needs to be analyzed. Several theories were hypothesized to explain this proposed linkage; however, none of them had a robust proof

Table 1: Descriptive demographic and bibliographic data of the studied patients (*n* = 16)

Studied variables	Mean	SD
Age (years)	56.63	6.79
Duration of HCV infection (years)	8.69	4.64
Timing of HCC presentation post treatment (months)	4.19	3.48
Gender	Number	Percent
Males	15	93.8
Females	1	6.2
HCV genotyping	All cases were genotype 4a	
Site of lesion(s) by ultrasound		
Right	10	62.5
Left	2	12.5
Multifocal	4	25.0
Size of the lesion(s) (cm)		
Less than 3	12	75.0
3-5	3	18.8
More than 5	1	6.2
Virological responses		
End of treatment	14	87.5
Sustained responders	13	81.3
Relapsers	1	6.2
Incomplete course	2	12.5
The DAAs' regimens		
Sofosbuvir + ribvirin	11	68.8
Sofosbuvir + simprevir	1	6.2
Sofosbuvir + daclatasvir	3	18.8
Sofosbuvir + daclatasvir + ribvirin	1	6.2

HCV: hepatitis C virus; HCC: hepatocellular carcinoma; DAA: direct-acting antiviral

Table 2: Descriptive laboratory data of the studied patients (*n* = 16)

Laboratory investigations	Before treatment	On HCC diagnosis
Total bilirubin (mg/dL)	0.80 ± 0.66	4.84 ± 2.14
Direct bilirubin (mg/dL)	0.50 ± 0.20	1.82 ± 1.68
AST (IU)	88.40 ± 34.34	79.00 ± 75.42
ALT (IU)	74.30 ± 23.60	74.63 ± 52.12
ALK (IU)	45.00 ± 17.25	172.25 ± 156.19
GGT (IU)	36.00 ± 12.00	69.06 ± 72.15
Serum albumin (mg/dL)	3.40 ± 0.50	2.20 ± 0.88
Hemoglobin (gm/L)	12.30 ± 2.20	11.81 ± 2.37
WBCs (10^3/L)	4.60 ± 6.10	8.63 ± 4.32
Platelet (10^3/L)	123.00 ± 32.50	102.50 ± 45.10
Prothrombin concentration (%)	87.20 ± 12.40	44.94 ± 25.47
INR(s)	1.20 ± 0.30	1.50 ± 0.46
Serum HCV-RNA average levels (IU)	517,229.10	
Serum AFP (ng/mL)	20.00 ± 12.46	479.46 ± 588.96

HCC: hepatocellular carcinoma; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALK: alkaline; GGT: gamma glutamyl transpeptidase; WBC: white blood cell; INR: international normalized ratio; AFP: alpha fetoprotein

of concept. DAAs induced HCV elimination with subsequent disturbance of immune functions and less anti-tumoral potency is the most proposed explanation for developing HCC. Also, deprivation of the hepatic microenvironment from the inflammatory scene containing endogenous IFN-inducible natural killer cell/cytotoxic T lymphocytes and many other antiviral tumor molecules; definitely has a pro-oncogenic effect.[9]

The reported downregulation of IFN and IFN stimulated genes following dual sofosbuvir-ribavirin induced viral eradication might add another explanation.[10] In pre-clinical studies, IFN alpha had demonstrated activity against several tumor types including HCC. Many reports had demonstrated the beneficial effects of IFN alpha in reducing incidence of HCC in cirrhotic patients who achieved sustained virological response. van der Meer *et al*.[11] in their sizeable multinational study, with longstanding follow-up periods had proved the positive effect of post IFN SVR on reducing morbidity and mortality and in diminishing HCC incidence rates in HCV-related cirrhosis patients. They reported that only 4% of those who achieved SVR had experienced HCC development against 76% in those who didn't.[11]

A recent systematic review had examined the HCC incidence in 5 randomized controlled trials (RCTs) including 1,926 chronic hepatitis C (CHC) patients with cirrhosis or advanced fibrosis has concluded that IFN-treated CHC cirrhotic patients showed a lower HCC incidence than non-IFN-treated controls after 5-years follow-up.[12] The same review examined the outcome of antiviral treatments in 6 RCTs with a total of 374 HCV-related HCC patients who had received curative therapy for HCC. After a more than 25 months (median) follow-up, IFN-treated patients showed a lower recurrence rate of HCC, than non-IFN-treated controls.[12]

Although the exact mechanism behind the anti-tumor properties of IFN has not been yet fully elucidated, it has been widely used for the treatment of numerous types of cancer, including certain hematological malignancies and solid tumors.[13] A recent *in vivo* study reported the IFN's ability to synergize the apoptotic, autophagic as well as the anti-proliferative action of cisplatin.[14] Autophagy has been shown to be induced in HCC cell lines when treated with IFN-α2b in a dose-dependent manner.[15]

Of note, autophagic cell death had been suggested as one of the anti-cancer actions of anti-cancer therapeutics.[16] Supporting these postulations was the recent study by Liang *et al*.[17] who concluded that treatment by pegylated IFN was associated with a lower HCC incidence than nucleos(t)ide analogues in chronic HBV infection. They described the oncogenic surface antigen truncation mutations to be detected in entecavir-treated patients with HCC but not in pegylated IFN-treated patients.[17]

Unlike IFN, DAAs have neither anti-angiogenic nor anti-proliferative properties and have no effect on oncogenic buds that already would reside cirrhotic livers.

For the time being, risk assessment for HCC should be rigorously undertaken before DAAs, and those at risk should have attentive surveillance during treatment and afterward. For people at risk, it is noteworthy to explain the importance of continued surveillance after HCV eradication. Also, physicians in the outreach clinics should know by heart that in HCV-positive patients, the risk of HCC is reaching higher figures compared with those eliminated the virus, yet sustained responders having advanced fibrosis are still at high HCC risk.

Liver fibrosis has been proven to be regressive in some patients who eliminated the virus;[18] hence post treatment transient elastography would be beneficial in defining patients within the surveillance program. Moreover, surveillance programs had to be strengthened by predictive genetic as well as

angiogenic HCC bio-markers.

In conclusion, surveillance programs should be widely endorsed during and after DAAs therapy for patients at HCC risk, even for those who had been achieved HCV cure. Perhaps IFN still has a role -- using it as a backbone therapy might benefit patients at the highest risk of HCC.

DECLARATIONS

Authors' contributions

Idea and study design: E.A. Rewisha
Collection of literature data: O. Elshaarawy, D.M. Elsabaawy
Data analysis: A. Abdelah
Clinical data collection, manuscript writing and critical revision: O.M. Alhaddad, M.M. Elsabaawy

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Conflicts of interest

There are no conflicts of interest.

Patient consent

A written informed consent was obtained from all participants in the study.

Ethics approval

The study protocol was approved by the Institutional Review Board (IRB) and local ethical committee of the National Liver Institute, Menoufia University.

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