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Efficacy and safety of direct-acting antivirals for HCV in patients with extrahepatic malignancies: real-life experience

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Abstract

Background: Outcome of HCV treatment with direct antiviral agents in malignant patients is questionable. The aim is to assess the safety and efficacy of DAAs in treatment of chronic HCV patients who received chemotherapy for malignancies.

Materials: Retrospective cohort study of 83 patients with HCV post chemotherapy receiving DAAs treatment compared to a matched group of 88 chronic HCV patients without cancer. Demographic, laboratory and abdominal ultrasound data, and SVR were taken for all patients.

Results: Patients' data revealed mean age (52 years) and BMI (29). A total of 52% of HCV patients were females, and 83.6% were treatment naïve. Patients with cancer had higher FIB4 values and more cirrhosis (20.5% vs. 13.6%) with no statistical significance. Total bilirubin and HbA1C levels were significantly higher in HCV patients without cancer. All patients in either groups received SOF-based DAAs except 2 cases received PAR/OMP/RBV. SVR rate was very high and comparable between the two groups (100% and 97.7% in post chemotherapy and control groups) with no statistical difference. Mortality was represented in 23% in patients post chemotherapy with FIB4 score considered the only predictor for mortality.

Conclusion: DAAs have excellent efficacy in patients post chemotherapy. Further studies should be conducted for their concomitant use with chemotherapy.

Keywords: HCV, Chemotherapy, Direct-acting antiviral

Introduction

Estimates of the prevalence of chronic HCV infection among patients with cancer in the USA range from 1.5 to 10.6% [1]. Studies show that HCV can negatively impact disease-specific mortality in patients with cancers [2, 3], and that early diagnosis with virologic cure on the other side improves liver and cancer outcomes and survival of patients with HCV-associated non-Hodgkin lymphoma and hematopoietic cell transplant (HCT) recipients [3].

Unfortunately, despite the increasing availability of safe and effective DAAs after 2013, there is an observed decrease from 54% of oncology clinical trials allowing access to patients with chronic HCV infection in 2013 to 44% allowing access in 2018. This may be related to the presence of many challenges concerning HCV treatment in the setting of cancer including the fear of an increased risk of liver disease progression, activation of concomitant HBV infection, occurrence of severe drug-drug interactions, and the absence of a standard of care to guide how and when to treat such patients [4]. However,

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several studies demonstrated safety of HCV treatment in cancer patients even when taken simultaneously with chemotherapy.

In Egypt, hepatitis C virus (HCV) infection represents a significant cause in liver-related morbidity and mortality [5]. The cornerstone for the hepatitis C model of care (MOC) in Egypt is the national committee for control of viral hepatitis (NCCVH), whose program is considered one of the most successful and effective public health programs [4].

According to NCCVH treatment protocol, chronic HCV patients with extrahepatic malignancies should not be treated except after 2 years of disease-free interval.

In the current study, we aimed to assess the safety and efficacy of DAAs in the treatment of chronic HCV patients who received chemotherapy for non-hepatic malignancies according to the NCCVH treatment protocol and to compare their results to a group of chronic HCV patients without history of cancer paving the way to challenge the use of these medications in patients under cancer therapy to improve patient's outcome.

Material and methods

Patient population

It is a retrospective cohort study of 83 Egyptian patients who underwent chemotherapy for extrahepatic malignancy receiving DAAs treatment for HCV and enrolled in the program of NCCVH in a period from 2015 to 2020 as regards treatment safety and efficacy compared to a matched group of 88 chronic HCV patients with no reported malignancy.

Inclusion criteria included adults more than 18 years old and of both sexes, patients with chronic HCV infection fulfilling the inclusion criteria for DAAs administration according to protocol of NCCVH, and patients with extrahepatic cancer with at least 2 years free of cancer after chemotherapy. Exclusion criteria included cancer patients on current chemotherapy, patients with HCC, and any patient with chronic HCV infection not fulfilling the inclusion criteria for DAAs administration according to protocol of NCCVH. This study was approved by the ethical committee. Direct-acting antiviral received according to NCCVH was as follows: sofosbuvir/daclatasvir, interferon/sofosbuvir/ribavirin, paritaprevir/ombitasvir/ribavirin, sofosbuvir/daclatasvir/ribavirin, sofosbuvir/paritaprevir/ombitasvir/ribavirin, sofosbuvir/ribavirin, and sofosbuvir/simeprevir.

Demographic data, baseline laboratory, and imaging tests

- Baseline demographic data including age, sex, and BMI were retrieved in addition to history of previous anti-HCV treatment.
- Past history including comorbidities such as diabetes and hypertension
- Clinical findings including signs of hepatic decompensation (jaundice, ascites, etc.)
- Baseline laboratory data including CBC with differential, CRP, PT, PC, and INR, liver biochemical profile: ALT and AST, bilirubin (total, direct), albumin, urea, creatinine, AFP, HBA1C in diabetics, and quantitative HCV PCR
- Abdominal ultrasound for detection of the presence of liver cirrhosis, HCC or ascites, or hepatic or nodal involvement with the tumor
- Transient elastography using FibroScan device whenever possible
- Revision of drug-drug interaction in patients on long-term anticancer therapy
- Eligibility for DAAs administration according to inclusion criteria set by NCCVH protocol

Follow-up visits and after end of treatment

- Detection of any adverse events from DAAs and any laboratory abnormalities during monthly visits
- Quantitative HCV PCR after 12 weeks of end of treatment to detect achievement of sustained virological response (SVR12) and mortality data of the studied group.

Statistical analysis

It is a retrospective cohort study. Sample size was not predetermined. The national database was explored for patients who have been treated, and their treatment outcome was valid. Patients with known previous treated malignancy were filtered and analyzed.

Data of patients with previously treated tumors and treated by chemotherapy were extracted from database of NCCVH with description of demographic and clinical data on baseline as well as data available on follow-up. Virological outcome of DAAs was described in frequency of responders and their percent. Comparison between this group of cancer patients and another age- and gender-matched control group was conducted. Events were reported whether during follow-up period by the patients themselves or by surveillance call of the studied patients. Survival analysis presented those events. Multivariate regression analysis was conducted for mortality. All other demographic and baseline clinical factors and the presence of extrahepatic malignancy were the independent factors.

In all tests, p-value was considered significant if less than 0.05. The study was approved by the ethical

committee of the Faculty of Medicine, Cairo University, Egypt.

Results

This is a retrospective study done on 171 Egyptian HCV patients who received HCV antiviral treatment according to protocol of the National Committee for Control of Viral Hepatitis (NCCVH) in a period from 2015 to 2020. Eighty-eight patients are without cancer and 83 patients post chemotherapy for different types of cancer. Demographic features, comorbidities, and treatment status are demonstrated in Table 1. A total of 52% of HCV patients were females, and 83.6% were treatment naïve. The mean age and BMI of HCV patients post chemotherapy were 52 years and 29, respectively.

HCV patients post chemotherapy were more treatment experienced than those without cancer (18.1% vs. 14.8%); however, no statistical difference was demonstrated between the two groups as regards demographic features, comorbidities, or treatment status. Among the included HCV patients, only 7 were tobacco smoker, 11 with hypertension, and 33 with diabetes.

The laboratory investigations and liver stiffness measurements in all HCV patients incorporated in this study are listed in Table 2. Patients with cancer had higher FIB-4 values and more cirrhosis (20.5% vs. 13.6%), although results were statistically nonsignificant. On the other hand, total bilirubin and HbA1C levels were significantly higher in HCV patients without cancer.

All patients in either groups received SOF-based DAAs, except two cases received PAR/OMP/RBV. Most of the HCV patients in our study received HCV treatment for 12 weeks (113 representing 66.1%), 55 HCV patients post chemotherapy, and 58 HCV patients without cancer. No statistical significant difference was observed between either groups receiving treatment for 12 or 24 weeks. None of patients discontinued treatment due to adverse events except one in the control group. Treatment decision and duration in both groups are demonstrated in Table 3.

SVR rate was very high and comparable between the two groups (100% and 97.7% in post chemotherapy and control groups, respectively) with no statistical difference as shown in Table 3.

Among 83 HCV patients post chemotherapy, 19 patients died with mortality representing 23%. In regression analysis in which mortality is the dependant factor, FIB-4 score was the only predictor for mortality as demonstrated in Table 4. Treatment outcome was excluded from analysis as all patients with mortality achieved SVR.

Discussion

Chronic hepatitis C virus infection represents a significant burden in patients with cancer. Studies show that HCV can negatively impact disease mortality in patients with cancers. Early diagnosis with virologic cure can improve liver and cancer outcomes and survival of patients with HCV-associated non-Hodgkin lymphoma and hematopoietic cell transplant (HCT) recipients [1–3].

The current study aimed at assessment of the safety and efficacy of DAAs in the treatment of chronic HCV patients who received chemotherapy for non-hepatic malignancies according to the NCCVH treatment

Table 1 Demographic features, comorbidities, and treatment status in both HCV patients post chemotherapy (cases) and HCV patients without cancer (controls)

	Groups of HCV patients		**Total**	***p*-value**
	Post chemotherapy ***N*** **(%)** **83 (48.5%)**	**Without cancer** ***N*** **(%)** **88 (51.5%)**	***N*** **(%)** **171(100%)**	
Gender				
Female	44 (53%)	45 (51.1%)	89 (52%)	0.806
Male	39 (47%)	43 (48.9%)	82 (48%)	
Age/years				
Mean ± SD	52 ± 14	51 ± 13		0.660
BMI				
Mean ± SD	29 ± 5	30 ± 6		0.406
Treatment status				
Treatment experienced	15 (18.1%)	13 (14.8%)	28 (16.4%)	0.560
Tobacco consumption	5 (6%)	2 (2.3%)	7 (4.1%)	0.216
Hypertension	5 (6%)	6 (6.8%)	11 (6.4%)	0.35
DM	20 (24.1%)	13 (14.8%)	33 (19.3%)	0.123

Table 2 Laboratory investigations, abdominal ultrasound, and liver stiffness measurements in both HCV patients post chemotherapy (cases) and HCV patients without cancer (controls)

	HCV patients post chemotherapy Mean ± SD	**HCV patients without cancer Mean ± SD**		***p*-value**
ALT (IU/L)	58.6 ± 37.36	58.7 ± 102.6		0.993
AST (IU/L)	59.6 ± 31.8	54.2 ± 55.6		0.440
Baseline HCV RNA × log 10	5.63 ± 0.91	5.54 ± 0.95		0.63
AFP (U/L)	10.8 ± 16.86	9.7 ± 15.13		0.712
Albumin (g/dl)	4.02 ± 0.65	3.99 ± 0.90		0.76
Total bilirubin (mg/dl)	0.80 ± 0.40	1.06 ± 1.17		**0.048**
Indirect bilirubin (mg/dl)	0.51 ± 0.42	0.50 ± 0.28		0.98
TSH	2.23 ± 1.8	1.74 ± 1.08		0.15
WBC × 10^3 mm^3	6.04 ± 3.98	7.13 ± 10.46		0.37
ANC × 10^3 mm^3	4.07 ± 8.21	6.51 ± 12.23		0.23
Hb (g/l)	13.22 ± 1.85	12.94 ± 1.50		0.27
Platelets × 10^3 mm^3	173.8 ± 71.8	184.83 ± 82.4		0.35
PC%	84.81 ± 16.36	86.37 ± 10.52		0.537
INR	1.12 ± 0.16	1.10 ± 0.13		0.38
Creatinine (mg/dl)	0.86 ± 0.26	0.91 ± 0.79		0.54
Glucose (mg/dl)	107.15 ± 31.66	109.52 ± 30.73		0.66
HbA1C%	6.34 ± 1.09	7.32 ± 1.46		**0.013**
Liver ultrasound known cirrhotic	*N* (%) 17 (20.5%)	*N* (%) 12 (13.6%)	Total 29 (17%)	0.233
Liver stiffness (Kpa)	15.28 ± 8.12	23.78 ± 16.77		0.28
FIB-4 calculation	3.14 ± 2.47	2.95 ± 3.06		0.655

$p \leq 0.05$ is significant

Table 3 Treatment decision, duration, and outcome in both HCV patients post chemotherapy (cases) and HCV patients without cancer (controls)

		Groups of HCV patients		**Total *N* (%) 171**	***p*-value**
		Post chemotherapy *N* (%) 83	**Without cancer *N* (%) 88**		
Treatment decision	IFN/SOF/RBV	12 (14.5%)	5 (5.7%)	17 (9.9%)	
	PAR/OMP/RBV	1 (1.2%)	1 (1.1%)	2 (1.2%)	
	SOF/DAC	18 (21.7%)	44 (50%)	62 (36.3%)	
	SOF/DAC/RBV	16 (19.3%)	20 (22.7%)	36 (21.1%)	
	SOF/PAR/OMP/RBV	1 (1.2%)	0 (0%)	1 (0.6%)	
	SOF/RBV	23 (27.7%)	18 (20.5%)	41 (24%)	
	SOF/SIM	12 (14.5%)	0 (0%)	12 (7%)	
Treatment duration	12 weeks	55 (66.3%)	58 (65.9%)	113 (66.1%)	0.961
	24 weeks	28 (33.7%)	30 (34.1 %)	58 (33.9%)	
Treatment outcome	SVR	83 (100%)	86 (97.7%)	169 (98.9%)	0.497
	Non SVR	0 (0%)	2 (2.3%)	2 (1.2%)	
	SVR	83 (100%)	86 (97.7%)	169 (98.9%)	0.385
	Relapser	0 (0%)	1 (1.1%)	1 (0.6%)	
	DC	0 (0%)	1 (1.1%)	1 (0.6%)	

SOF Sofosbuvir, *RBV* Ribavirin, *INF* Interferon, *SIM* Simeprevir, *DAC* Daclatasvir, *PAR/OMP* Paritaprevir/ombitasvir, *DC* Discontinue

Table 4 Logistic regression for mortality

Risk factors	*p*-value	*OR*	95% *CI* for *OR*	
			Lower	Upper
Age	0.22	2.15	0.64	7.27
Female gender	0.38	0.54	0.14	2.10
FIB-4	**0.006**	4.14	1.49	11.49
Albumin < 3.5	0.89	1.11	0.26	4.75

$p \leq 0.05$ is significant

protocol and to compare their results to a group of chronic HCV patients without history of cancer.

In this study, all HCV patients received SOF-based DAAs except only 2 patients who received PAR/OMP/RBV, and this was according to the program of NCCVH at Egypt. SVR was observed in all HCV patients post chemotherapy, none of them discontinued treatment, and only 2 HCV patients without cancer did not achieve SVR (1 relapsed and 1 discontinued). Univariate analysis for factors associated with treatment failure revealed nonsignificant results.

Although patients in our study received DAAS therapy after 2 years of cancer-free status as per NCCVH protocol, other studies as that done by Economides et al. in 2016 suggested safe simultaneous administration of DAAs and chemotherapy in 21 HCV-infected cancer patients (solid or hematological malignancies); no clinically significant drug-drug interactions between DAAs and chemotherapy were observed. Chemotherapy was not discontinued for any patient receiving concomitant DAA therapy with no deaths reported during the study [6].

Another study supported the idea of DAAs in cancer patients where Persico et al. in 2018 found that in HCV-infected patients with diffuse large B-cell lymphoma, disease-free survival was better in patients receiving DAAs than in untreated patients after 52 weeks of follow-up, and antiviral therapy was an independent predictor of better disease-free survival [7].

Treatment of HCV in cancer patients was also recommended by a study done by Tores et al. in 2018 where HCV reactivation and hepatitis flare were observed during chemotherapy in patients with HCV which required discontinuation or dose reduction of chemotherapy. However concomitant use of DAAs with chemotherapy should not be offered if toxic effects from this overlap can occur [8–10].

Mortality was observed in 23% of HCV patients post chemotherapy. Merli et al. in 2019 reported 2-year survival rate of 97.4% in patients with diffuse large B-cell lymphoma [11]. Higher mortality rate in our study may be related to having various types of cancer and performing the analysis on longer follow-up period (up to 5 years).

In our cohort, FIB-4 was the only predictor for mortality in HCV patients post chemotherapy. Xu et al. in his study on 2799 HCV-mono-infected patients who had a liver biopsy results concluded that the risks of death and progression to liver failure varied greatly by fibrosis stage, and that policy makers could use these progression risk data in prioritization of treatment for patients with liver disease [12].

In the current study, we observed higher mean age (52 years old) in group of HCV patients post chemotherapy. This may be explained by cancer research in UK where they found that age-specific incidence rates rise steeply from around age 55–59 with a conclusion that adults aged 50–74 accounted for more than half (54%) of all new cancer cases (https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero).

As we evaluated the liver condition for HCV patients encountered in our study, patients with cancer had higher FIB-4 values and more cirrhosis than those without cancer; this was supported by the fact that patients with liver cirrhosis bear a higher risk not only for liver cancer but also for extrahepatic malignancies compared to the general population, and that common habits among the general population like tobacco, alcohol abuse, and the metabolic syndrome represent risk factors for both cancer and cirrhosis [13–18].

It was observed that HCV patients post chemotherapy had lower liver stiffness by FibroScan and higher FIB-4 values than those without cancer and without statistical significance; this may be due to the presence of lower platelets count due to chemotherapy.

All initial laboratory data were found to be of no significant difference between both HCV groups encountered in our study except for statistically higher bilirubin and HbA1c in HCV group of patients without cancer, although DM was observed more in patients post chemotherapy than those without cancer (24.1 vs. 14.8%); this was supported by the epidemiologic evidence that diabetes is associated with an increased risk of cancer [19, 20]. The lower levels of HbA1C in post-chemotherapy HCV patients were against the study done by Hershey et al. in 2014 which concluded that chemotherapy and associated symptoms can have a negative impact on the performance of diabetes self-management activities in adults with both diabetes and cancer, increasing the risk for hyperglycemia and development of complications [21].

To our knowledge, this study is among the fewest studies which assessed the efficacy and safety of DAAs for treatment of HCV among cancer patients who received chemotherapy from different non-hepatic malignancies.

Main limitation of the current study is its retrospective nature with lack of data on oncological outcome in patients post chemotherapy.

Conclusion

HCV therapy in post-chemotherapy patients is highly effective and safe and should be challenged in larger prospective studies to be given simultaneously with chemotherapy to offer better hepatic and patient outcome.

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Authors' contributions
MA, drafting of the paper, conception, and design. RE, conception and design and revision of the draft. MA, supervision of clinical center with data collection. RS, designing and drafting for the cancer and chemotherapy section. WE, analysis and interpretation of the data. MH, supervision of clinical center. WAR, supervision of clinical center. YE, supervision of clinical center. WD, supervision of clinical center. GE, final approval of the version to be published and supervision of clinical center. All authors agree to be accountable for all aspects of the work. The authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare that they have no competing interests.

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