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ORIGINAL ARTICLE

Risk of Hepatocellular Carcinoma Development in Chronic Hepatitis C Patients Who Achieved a Sustained Virological Response With Interferon-Based Treatments

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Abstract

Introduction: We aimed to evaluate hepatocellular carcinoma (HCC) risk in patients who achieved an sustained virological response (SVR) with interferon (IFN)-based treatments at long-term follow-up.

Methods: In this retrospective study, we reviewed the data of patients with Chronic hepatitis C who received IFN-based treatments between January 2004 and July 2015 and had achieved SVR. Eighty-two patients who met the inclusion criteria were included in the study. Laboratory test results, liver biopsy results, and imaging findings at the start of treatment were recorded. Serum HCV RNA results at the start, the end and the 24th week after completion of treatment, and HCV genotype were also recorded. Follow-up was the time interval between the end of therapy and HCC diagnosis or the date of last available imaging in the absence of HCC. When any new lesion has appeared on USG, then patients underwent triphasic computed tomography or dynamic magnetic resonance imaging. HCC was diagnosis according to guidelines.

Results: In our cohort, 10 (12%) patients had advanced fibrosis or cirrhosis. After 88 months of mean follow-up duration, 3 of 82 (3.7%) patients developed HCC. The mean time between the end of treatment and HCC development was 91 months. Two patients who developed HCC had cirrhosis, while 1 had F1 fibrosis at the start of treatment. However, the noncirrhotic patient had concomitant nonalcoholic liver disease and developed cirrhosis during follow-up, and had cirrhosis at the time of HCC diagnosis. One patient had genotype 1 and one had genotype 2 HCV, while genotype was not determined in 1 patient. Two of these patients had diabetes mellitus.

Discussion and Conclusion: HCC can be developed even in patients who achieved an SVR after years of IFN-based treatments. Particularly, patients with advanced fibrosis or cirrhosis must be under surveillance for HCC indefinitely. Patients with no-mild fibrosis should also be under surveillance for HCC if they had another risk factors for cirrhosis.

Keywords: Hepatitis C; Hepatocellular carcinoma; Interferon.

Chronic hepatitis C (CHC) is one of the leading causes of cirrhosis, decompensation, hepatocellular carcinoma (HCC), liver transplantation, and liver-related mortality. At present, direct-acting antivirals (DAAs) are the mainstay of CHC treatment [1]. However, interferon (IFN)-based treatment modalities were widely used for the treatment

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of CHC before the advent of DAAs. IFN-based treatments were not as effective as DAAs. Sustained virological response (SVR) rates were low particularly in genotype 1b, which is the most common genotype in Türkiye [2]. IFN-based treatments were also associated with adverse effects and were contraindicated in patients with decompensated cirrhosis [3].

It has shown that the risk of cirrhosis and HCC decreased in patients who achieved an SVR with IFN-based treatments [4]. However, HCC risk is not totally eliminated. According to current guidelines, ultrasonography (USG)±serum alfa-fetoprotein (AFP) measurement at every 6 months is the recommended HCC surveillance strategy in patients who are at risk for HCC. Particularly patients with advanced fibrosis or cirrhosis are at risk for HCC. So, patients with cirrhosis at baseline should be under surveillance for HCC. According to current guidelines, patients with bridging fibrosis (F3) or advanced fibrosis (F4) should also be under surveillance for HCC, while it is not recommended for patients with no-mild fibrosis (F0-2) [5].

However, lifelong surveillance has a substantial economic burden on health-care systems. Moreover, it also has psychological effects on patients [6]. Long-term results of HCC surveillance are limited in patients who achieved an SVR with IFN-based treatment [7]. The regression of fibrosis after SVR has been shown in several studies [8]. Therefore, with the regression of fibrosis over time, it can be expected that the risk of HCC will decrease and HCC surveillance will become unnecessary. Unfortunately, there is not enough study that shows the correlation between the regression of fibrosis and decreased HCC risk [9]. So, there is need for studies to determine how long these patients should remain under HCC surveillance. Moreover, most of the patients who achieved an SVR with IFN-based treatments are young and have low stages of fibrosis. Hence, there is also a need for studies evaluating HCC risk in those patients without cirrhosis.

In this study, we aimed to evaluate HCC risk in patients who achieved an SVR with IFN-based treatments at long term follow-up.

Materials and Methods

In this retrospective study, we reviewed the data of patients with CHC who received IFN-based treatments between January 2004 and July 2015 and had achieved an SVR. Eighty-two patients who met the following criteria were included in the study. The inclusion criteria were as follows: (1) age ≥18 years, (2) anti HCV and HCV RNA positivity for ≥ 6 months before treatment, (3) treatment with IFN-ribavirin±telaprevir/boceprevir, (4) negative HCV RNA results at the end of therapy and the 24th week after completion of treatment, (5) absence of coinfection with hepatitis B virus and/or human immunodeficiency virus, (6) absence of any other etiology for chronic liver diseases, and (7) available imaging results after ≥6 months at the end of treatment. The exclusion criteria were as follows: (1) age <18 years, (2) coinfection with hepatitis B virus and/or human immunodeficiency virus, (3) presence of any other etiology for chronic liver diseases, and (4) history of HCC and/or liver transplantation before the start of treatment.

Laboratory test results (serumAST, ALT, ALP, GGT and albumin, bilirubin, AFP, PT, INR, and platelet levels), liver biopsy results (if available), and imaging findings at the start of treatment were recorded. Serum HCV RNA results at the start, the end and the 24th week after completion of treatment, and HCV genotype were also recorded.

Cirrhosis was diagnosed radiologically, endoscopically, and/or histologically. Radiologically, presence of nodular appearance and irregularity on liver surface, elevated portal vein diameter or splenomegaly on USG were defined as cirrhosis. Endoscopically, patients with esophagogastric varices on endoscopy were considered as having cirrhosis. Histologically, no-mild fibrosis was defined as F0-2, significant fibrosis as F3, advanced fibrosis as F4 and cirrhosis as F5-6 fibrosis according the Ishak system [10].

Patients received IFN-ribavirin±telaprevir/boceprevir according to the published guidelines [11]. SVR was defined as negative HCV RNA at 24th week after completion of treatment.

Follow-up was the time interval between the end of therapy and HCC diagnosis or the date of last available imaging in the absence of HCC.

When any new lesion has appeared on USG, then patients underwent triphasic computed tomography or dynamic magnetic resonance imaging. HCC was diagnosis according to guidelines [12].

Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2016. Quantitative variables were presented as means (±SD), standard deviation and percentages.

The study was carried out in accordance with the Helsinki Declaration and approved by the local ethics committee (approval no: 771/11/2020-4). Informed consent was not obtained due to the retrospective design of the study.

Results

The study included 82 patients. The mean age of the patients was 50.40±11.21 years and 44 (53.7%) of them were male. The mean body mass index was 29.22±4.63 (17.29–29.16) kg/m^2. The mean serum HCV RNA level was 3,496,736.65±6,450,573.22 IU/ml. Of the patients, 61 (74.4%) were infected with genotype 1 HCV, 3 (3.7%) with genotype 2 and 5, and (6.1%) with genotype 3. In 13 patients, genotype was not determined and they were treated as if they had genotype 1 HCV. Of the 66 patients with available liver biopsy results, 7 (8.5%) had F3, 1 (1.2%) had F4 and 9 (11.0%) had cirrhosis. None of the patients, who did not undergo liver biopsy, had cirrhosis based on USG (Table 1).

Of the patients, 77 (93.90%) received IFN+ribavirin, 4 (4.87%) received IFN+ribavirin+telaprevir and 1 (1.25%) received IFN+ribavirin+boceprevir.

Laboratory test results at the start of therapy are shown in Table 2.

The mean follow-up duration was 88.35±40.35 (6–167) months. Three (3.7%) patients developed HCC. The mean time interval between the end of treatment and HCC diagnosis was 91 months. Of them, 2 were male and 1 was female. Two male patients had cirrhosis at baseline, while the female patient had F1 fibrosis. Two patients who underwent liver transplantation and TACE for HCC therapy were still alive, 1 patient who received sorafenib died (Table 3).

At follow-up, seven patients died. Six of them died due to non-liver related causes. The cause of mortality was coronary heart disease in two patients, lung cancer in two patients, pancreas cancer in 1 patient and gastrointestinal stromal tumor in one patient.

Table 1. Demographic and laboratory data of patients

Age (mean±SD, range)	50.40±11.21 (21–75)
Gender (Male, %)	44 (53.7%)
BMI (mean±SD, kg/m^2, range)	29.22±4.63 (17.29–29.16)
HCV RNA (IU/mL) (mean±SD)	3,496,736.65±6,450,573.22
Genotype, n (%)	
G1	61 (74.4)
G2	3 (3.7)
G3	5 (6.1)
Unknown	13 (15.8)
Cirrhosis n (%)	9 (11)
Stage of fibrosis, n (%)	
F0	12 (14.6)
F1	15 (18.3)
F2	22 (26.8)
F3	7 (8.5)
F4	1 (1.2)
F5	1 (1.2)
F6	8 (9.8)
Unknown	16 (19.5)
Treatment, n	
PEG-IFN alfa 2a/2b+Ribavirin	77
PEG-IFN alfa 2a/2b+Ribavirin+Telaprevir	4
PEG-IFN alfa2a/2b+Ribavirin+Bocepravir	1
Follow up (Months) (mean±SD, range)	88.35±40.35 (6–167)
HCC, n (%)	3 (3.7)
Overall deaths/liver-related deaths	7/1

SD: Standard deviation; HCC: Hepatocellular carcinoma; BMI: Body mass index; PEG-IFN: Pegylated interferon.

Table 2. Laboratory test results at the start of therapy

AST (IU/mL) (mean±SD, range)	56.57±42.73 (19–259)
ALT (IU/mL) (mean±SD, range)	74.67±57.98 (17–335)
GGT (IU/mL) (mean±SD, range)	51.08±47.91 (10–330)
ALP (IU/mL) (mean±SD, range)	89.22±39.57 (41–331)
Total bilirubin (mg/dL) (mean±SD, range)	0.92±1.04 (0.19–9.21)
AFP (ng/mL) (mean±SD, range)	7.77±26.83 (0.25–235.36)
INR (mean±SD, range)	1.06±0.29 (0.85–2.73)
Albumin (gr/dL) (mean±SD, range)	4.20±0.31 (3.4–5.2)
Platelet (×10^3/μL) (mean±SD, range)	214.43±63.64 (61–420)

SD: Standard deviation; AST: Aspartate transferase; ALT: Alanine transferase; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase; AFP: Alpha fetoprotein; INR: International normalized ratio.

Discussion

The risk of HCC is significantly reduced in CHC patients who achieved an SVR with IFN-based treatments compared with those who did not achieved an SVR [13,14]. The risk of HCC development increases with advancing stage of fibrosis. In cirrhotic CHC patients, the annual HCC risk is 1–4% [15]. Therefore, close follow-up is strictly recommended in CHC patients with advanced fibrosis and cirrhosis even if they achieved an SVR. It is also recommended in those patients with bridging fibrosis since it is difficult to differentiate between stages F3 and F4 fibrosis. On the other hand, there is controversy whether patients with F0-2 fibrosis should also be under close follow-up [6].

In the present study, we evaluated the risk of HCC development in CHC patients who achieved an SVR with IFN-based treatments. In our cohort, 10 (12%) patients had advanced fibrosis or cirrhosis. After 88 months of mean follow-up duration, 3 of 82 (3.7%) patients developed HCC. The mean time between the end of treatment and HCC development

Table 3. Demographic and laboratory data of hepatocellular carcinoma patients

	Patient 1	Patient 2	Patient 3
Gender	Female	Male	Male
BMI (kg/m^2)	27.89	25.76	20.90
HCV RNA (IU/mL)	2887529	1100000	46893
HCV Genotype	1b	Unknown	2
Stage of fibrosis	1	6	6
Steatosis, %	10%	25%	Unknown
Anti HBcIg G	Negative	Negative	Negative
AFP at treatment onset (ng/mL)	Unknown	4.03	235.36
Diabetes mellitus	Yes	No	Yes
Age at treatment onset (years)	57	49	53
Age at HCC diagnosis (years)	66	58	61
Time to HCC after treatment (months)	98	91	84
HCC treatment	Sorafenib	TACE	Liver transplantation
Outcome	Death	Live	Live

BMI: Body mass index; anti HBcIgG: Antibody to hepatitis B core antigen Ig G; AFP: Alpha fetoprotein; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization.

was 91 months. Two patients who developed HCC had cirrhosis, while 1 had F1 fibrosis at the start of treatment. However, the noncirrhotic patient had concomitant nonalcoholic liver disease and developed cirrhosis during follow-up, and had cirrhosis at the time of HCC diagnosis. One patient had genotype 1 and one had genotype 2 HCV, while genotype was not determined in one patient. Two of these patients had diabetes mellitus.

To date, several studies have been conducted to evaluate long-term outcomes of CHC patients who achieved SVR with IFN-based treatments. In the study by Nagaoki et al., [16] 36 of 1094 (3%) patients developed HCC after a mean follow-up of 50 months. In that study, only 3.1% of patients had cirrhosis and 53% had genotype 1 HCV. The mean time to HCC development after treatment was 37 months. In the study by Yamashita et al., [17] 31 of 562 (5.5%) developed HCC after a mean follow-up of 58 months. Unlike the previous study, 9% of patients had cirrhosis and a significant proportion of patients who developed HCC (45%) had stage F1 and F2 fibrosis at the start of treatment. In these studies, the risk factors for HCC development were advancing fibrosis stage and advancing age (over 50–60 years) [16,17]. Consistent with these results, HCC was developed in 1.7% of patients with stage F1-2 fibrosis and 3.7% of patients with stage F3-4 fibrosis [18]. Yamashita et al. [17] showed alcohol consumption ≥30 g/day as a risk factor HCC development and Nagaoki et al. [16] did male gender. AFP ≥8 ng/ml at the start of treatment was associated with HCC development in the study by Yamashita et al., [17] while AFP≥10 ng/ml 1 year after treatment was associated with HCC development in the study by Nagaoki et al. [16].

Unlike the above-mentioned studies, most of the patients were infected with genotype 1 HCV in our cohort. Moreover, the proportion of patients with cirrhosis was higher, the patients were younger and the follow-up duration was longer in our study. However, the incidence of HCC was similar to these studies in our cohort.

In a recently published study by Özdoğan et al., [19] HCC developed in 1 of 135 (0.7%) Caucasian patients who were mostly infected with genotype 1 HCV Genotype, prevalance of cirrhosis and ethnicity were similar to our cohort. The higher HCC incidence in our cohort might be due to higher number of male patients and higher age of patients compared with that study.

Van der Meer et al. [20] included only those patients with advanced fibrosis or cirrhosis in their study. In that study, 7 of 125 (5.6%) patients developed HCC after a mean follow-up of 101 months and the mean time to HCC development was 82 months after treatment. Of the patients, 42% had genotype 1 HCV, 9% had diabetes mellitus, and 26% had heavy alcohol consumption. Moreover, they found that all-cause mortality were associated with advanced age, genotype 3, high stages of fibrosis, diabetes mellitus, and heavy alcohol consumption.

El-Serag et al. [21] evaluated 10,738 veterans who achieved SVR with IFN-based treatments. The most striking point of this study is that 95% of the patients were male. At the

start of treatment, 54% of the patients were infected with genotype 1 HCV and 14.4% had cirrhosis. HCC developed in 100 (0.9%) patients. In the multivariate analysis, age over 55 years, diabetes mellitus, genotype 3, heavy alcohol consumption, and Hispanic ethnicity were significant predictors for HCC. However, the mean follow-up time was significantly shorter than previous studies.

The most important limitation of the present study is small sample size compared with previous studies. Another limitation of the study was lack of information about alcohol consumption and the presence of diabetes mellitus. However, the mean follow-up duration was longer in our study. We also included both noncirrhotic and cirrhotic patients.

Conclusion

HCC can be developed even in patients who achieved an SVR after years of IFN-based treatments. Particularly, patients with advanced fibrosis or cirrhosis must be under surveillance for HCC indefinitely. Patients with no-mild fibrosis should also be under surveillance for HCC if they had another risk factors for cirrhosis.

Ethics Committee Approval: The study was carried out in accordance with the Helsinki Declaration and approved by the local ethics committee (approval no: 771/11/2020-4).

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