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Frequency of hepatocellular carcinoma in patients with hepatitis C received treatment with directly antiviral agents

Dr Ubedullah Bughio

Senior Registrar, Asian Institute of Medical Science Hyderabad, Sindh, Pakistan

Dr Adil Hassan Chang

Senior Registrar, Asian Institute of Medical Science Hyderabad, Sindh, Pakistan

Dr Rahmatullah Bhatti

Assistant Professor, Asian Institute of Medical Science Hyderabad, Sindh, Pakistan

Dr Bushra Kadir

Senior Registrar, Asian Institute of Medical Science Hyderabad, Sindh, Pakistan

Dr Muhammad Sadik Memon

Professor, Asian Institute of Medical Science Hyderabad, Sindh, Pakistan

Dr Saadat Ali

Assistant Professor, Asian Institute of Medical Science Hyderabad, Sindh, Pakistan

Dr Mashooque Samejo

Resident, Asian Institute of Medical Science Hyderabad, Sindh, Pakistan

Dr Sidra Dars

Resident, Asian Institute of Medical Science Hyderabad, Sindh, Pakistan

Abstract---Background and Aims: Hepatitis C infection is one of leading causes of liver cirrhosis and a considerable proportion of hepatocellular carcinoma worldwide. Despite the very high efficacy of Directly Acting Viral Agents (DAAs) on clearance of hepatitis C their role remains controversial on development of Hepatocellular Carcinoma. The Aim of this study is to analyze hepatocellular occurrence in hepatitis C patients after achieving Sustained virologic response on directly acting viral agent. Methods and Material: It is prospective study conducted on outpatients in the Hepato-gastroenterology department of Asian Institute of Medical Science

Hospital Hyderabad from 21-10-2018 to 20-04-2019. All patients who fulfilled the criteria were enrolled, their baseline demographic characteristics, Child Pugh Class, MELD score, alpha-fetoprotein level and Ultrasound liver before and after treatment collected. Duration of DAAs treatment and type of DAAs used also noted. Hepatocellular carcinoma labelled when Triphasic CT scan liver shows typical characters of hepatocellular carcinoma i.e. arterial phase hyperenhancement and delayed washout on portal and venous phase or ultrasound liver shows focal liver lesion with alpha-fetoprotein level more than 300ng/ml. Results: One hundred fifty-seven patients of chronic hepatitis C enrolled in the study after exclusion criteria. The mean age of the patients was 44.6 ± 11.434 years. Out of them 91 (58%) were males and 66 (42%) were females. Sixty-seven (48.4%) patients were Chronic Hepatitis C patients (non- cirrhotic), fifty-one (32.5%) were compensated CLD and thirty (19.1%) patients were decompensated CLD. Hepatocellular carcinoma was found in eight (5.1%) patients p value was 0.168 which was statically not significant after adjusting age, gender, Child Pugh Score, MELD score duration of treatment and severity of cirrhosis. Conclusion: Directly acting viral agents were not associated with increased risk of hepatocellular carcinoma. Although duration was only 6 months, longer duration may be needed.

Keywords---Hepatitis C, Hepatocellular Carcinoma, Directly Acting Viral Agents, Sustained virologic Response.

Introduction

Infection with the hepatitis C virus (HCV), which affects nearly 170 million people globally, is a key contributor to chronic liver disease (CLD). HCV is an encapsulated virus having 9.6 kb single-stranded RNA genome that was first discovered in 1989. It belongs to the Flaviviridae family, genus Hepacivirus [1]. About 16% of patients with HCV who have had it for longer than 20 years develop cirrhosis. Once cirrhosis has taken hold, the risk of hepatocellular carcinoma (HCC) and hepatic decompensation are both estimated to be 3-5% and 3-6%, respectively, per year. Additionally, 15-20% of people will pass away within a year after hepatic decompensation [2].

One of the top causes of death from cancer worldwide is hepatocellular carcinoma. Although HCV alone may have pro-carcinogenic qualities, cirrhosis is a significant risk factor for the development of HCC in those who have the infection. [3] The length of fibrosis, age, sex, platelet counts, and levels of HCV-RNA are among factors that have been associated to an increased risk of developing hepatocellular carcinoma. [4] Numerous studies have demonstrated that the incidence of HCC is decreased to 0.5%–1% annually after attaining sustained viral response (SVR) with interferon (IFN) therapy [5-7]. Initially, it was thought that IFN had direct anti-tumor effects in addition to antiviral ones that lowered risk, but non-sustained IFN responders did not have the same reduction

in HCC risk [8]. So it was assumed that it's not the IFN but the SVR reduce the risk and delays the progress of Hepatocellular Carcinoma.

Understanding the structure of HCV protease and polymerase has facilitated the development of inhibitors of these enzymes through structure-based drug design. All of the HCV enzymes, including the NS2-3 and NS3-4a proteases, NS3 helicase, and NS5b RDRP, are crucial for HCV replication and may one day be the subject of pharmaceutical research. As a result, various direct antiviral medicines were created, including NS3 protease inhibitors, RNA-dependent RNA polymerase inhibitors, nucleoside/nucleotide analogues, and NS5A inhibitors. These regimens shorten the course of treatment to 12 weeks or less while increasing the sustained virologic response (SVR) rates to above 90%. [1] It has been demonstrated that patients receiving DAAs have lower rates of decompensation and MELD score progression than those receiving standard care[9,10]. Few investigations conducted recently on a global scale revealed an elevated risk of hepatocellular carcinoma development and recurrence in patients receiving directly acting antiviral medicines., Reig et al [11] showed unanticipated surge of 27.6% HCC recurrence in patients of HCV treated with direct antiviral agents after HCC treated with loco regional treatment. Another study performed in Austria by Kozbial et al [12] showed increased incidence of HCC of about 6.6%, and in Portugal by Cardoso H et al [13] showed raised occurrence of about 7.4% HCC after the using direct antiviral agents in first year. Another study performed in Italy by In HCV-related cirrhosis treated with direct-acting antivirals, Buonfiglioli et al. [14] found that hepatocellular carcinoma occurred in 3.16% of cases and recurred in 28.81% of cases. A contrary finding from the Chinese study by Zeng QL et al. [15] points to a modest decline in the incidence rate. Another investigation carried out by Kanwal f et al [16] also found decreased incidence of hepatocellular carcinoma less than 1% after the use of direct antiviral agents.

HCV treatment has evolved from Ribavirin to Interferon to directly acting antiviral agents. Considering the clinical proof that direct antiviral agents are associated with hepatocellular carcinoma¹¹⁻¹⁴ if the association proves than policy makers could recommend screening of all candidates of directly acting antiviral agents with alpha fetoprotein and Ultrasound. They would recommend becoming vigilant on those patients who are already taking direct antiviral agents. Furthermore, a considerable number of patients can be prevented from hepatocellular carcinoma, its consequences and expenses which will be liable on these patients in future. Therefore, the purpose of this study was to determine how frequently hepatitis C patients receiving directly acting antiviral medications developed hepatocellular carcinoma.

Methods and Material

It is prospective, observational, single centered study conducted at hepatology division of Asian Institute of Medical Science Hospital Hyderabad, Sindh, Pakistan from 21st October 2018 to 20th April 2019. All patients with Hepatitis C virus (HCV) after achieving sustained virologic response with directly acting viral agents (DAAs) treatment were followed for six months to see the early occurrence of hepatocellular carcinoma. Their baseline characteristics, Child Pugh Class, MELD score, alpha-fetoprotein level and Ultrasound liver before and after treatment

collected. Duration of DAAs treatment and type of DAAs used also noted. Hepatocellular carcinoma labelled when Triphasic CT scan liver shows typical characters of hepatocellular carcinoma i.e. arterial phase hyperenhancement and delayed washout on portal and venous phase or ultrasound liver shows focal liver lesion with alpha-fetoprotein level more than 300ng/ml. All the data collected through structured proforma; SPSS 20 software used for data analysis.

Results

From 21st October 2018 to 20th April, 157 hepatitis C infected patients after achieving SVR with directly acting viral agents' treatment were enrolled. Table 1 shows cohort baseline demographic and clinical characteristics. Mean age was 44.62± 11.434. Male ratio was 58% and 42% were female. Seventy-six (48.8%) patients have no cirrhosis, while 51 (32.5%) were compensated cirrhosis and 30 (19.1%) have history of decompensation. From patients with cirrhosis 31.8% have CTP (A), 14.0% have CTP B and 5.7% have CTP C Maximum Model for End stage Liver Disease was 16. Eighty patients received directly acting agents for 12 weeks while 77 patients received 24 weeks treatment. Only eight patients developed hepatocellular carcinoma during follow up of 6 months.

Discussion

One of the most common causes of chronic liver illness is the hepatitis C virus (HCV), a hepatotropic RNA virus. A serious consequence of HCV virus infection that has high mortality and morbidity rates is hepatocellular carcinoma (HCC). The length of the illness and the viral genotype play a role in the HCC development caused by HCV [17]. Eliminating the infection, lowering the rate of transmission to others, and lowering the risk of developing HCC are the three objectives of HCV treatment. [18] The use of direct-acting antiviral (DAA) medications has become increasingly popular as a therapy option due to its high sustained virologic response (SVR) rates. [19] The incidence and morbidity of HCV-related HCC remain high even in the face of highly efficient treatment. According to long-term follow-up studies, 3-8% of cirrhotic patients who have HCV infection develop HCC each year, or around 1-8% of people with cirrhosis overall. [20]

With scanty and conflicting data on the association of HCC with DAA therapy, performed this cross-sectional study to examine the frequency of Hepatocellular carcinoma among HCV-infected chronic hepatitis C (noncirrhotic) and cirrhotic (compensated and decompensated) patients after achieving SVR with directly acting viral agents within 6 months. One hundred seven patients enrolled in the study after exclusion criteria at hepato-gastroenterology department of Asian Institute of Medical Science hospital Hyderabad from 21-10-2018 to 20-04-2019. Hepatocellular carcinoma was found in 8 (5.1%) more common in males (87.5%) and decompensated CLD (50%). When compared to historical rates, there was often no discernible difference in the rates of HCC in individuals receiving DAA-containing medication.

After treatment with directly active viral medicines, the current investigation found no increase in the incidence of hepatocellular disease in Hepatitis C

patients. This finding is in line with a study by Zeng QL et al. [15] in China, which showed a decreased incidence of hepatocellular carcinoma after DAAs therapy. This study's findings are also in line with a study by Kanwal f et al. [16] which showed a decreased incidence of hepatocellular carcinoma following SVR after DAAs treatment. Additionally, there is a difference in the risk of hepatocellular carcinoma following SVR between The results of our study do not agree with those of Kozbial et al (12), Cardoso H et al (13) and Ravi S et al [21] show raised incidence of hepatocellular carcinoma after the use of direct antiviral agents. Major difference in current study and studies done by Kozbial et al (12), Cardoso H et al (13) and Ravi S et al [21] is that included only cirrhotic patients and they were followed for longer duration except Ravi S et al [21] who's median follow up was 6 months as of current study. However, a meta-analysis that included 26 studies (11 523 patients) on the development of HCC after DAA therapy in patients with chronic HCV and cirrhosis (IFN = 17, DAA = 9; prospective = 19, retrospective = 5, retrospective-prospective = 2) found no evidence that DAA therapy was linked to a higher rate of HCC development. These findings are in line with the results of the current study.

Strength of our study was use of consecutive sampling best suited for our study design, first study on this topic in south Asia, patient selection criteria exclusion of all patients with possible risk factor for hepatocellular carcinoma, sample size calculation. Imaging and alpha-fetoprotein level before and after SVR.

Study Limitations

The primary limitations of the current study include its nonrandomized study design, single-center experience, young age representation in the study cohort, and cross-sectional design, where cause cannot be assigned. As a result, the figure does not accurately represent the disease's prevalence and severity. Second, some confounding variables were present in this trial, including age, the length of DAAs, the severity of cirrhosis, smoking, and others. Not all of the studies that were generated were altered. The results of this study may not be generalizable to wider populations because it used a limited sample size and an urban setting.

Conclusion

However, it was observed that patients with decompensated cirrhosis had a considerably higher incidence of developing HCC than those without the disease. In conclusion, our study did not discover a rise in the proportion of HCV patients with hepatocellular carcinoma who received DAA-containing medication over a 6-month monitoring window in comparison to earlier rates. Because patients with more severe liver disease can now receive treatment, whereas decompensated cirrhotic individuals were excluded from early interferon studies, rates of HCC may have increased in the era of DAA treatment. The continued need for routine HCC surveillance in HCV cirrhotic patients following antiviral therapy is supported by these information.

Age	44.62 ±11.434
Gender	M=91(58%) F= 66(42%)
Smoker	2(1.5%)
Cirrhosis	NO=76(48.4%) Yes=81(51.6%)
CTP Score	CTP A=50(32%) CTP B=21(13.4%) CTP C=10 (6.4%)
MELD	≤ 9= 128 (81.5%) 10-19= 28 (17.8%) ≥20=1(0.6%)
DM	17(10.8%)
Duration of DAAs	12 weeks 80(51%) 24 weeks 77(49%)

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