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Research Article

Characteristics and Survival during Hepatocellular Carcinoma: Comparison between Hepatitis B and C Viruses

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Abstract

Introduction: Chronic hepatitis B and C remain the leading causes of cirrhosis and Hepatocellular Carcinoma (HCC) in Africa and South East Asia. In Tunisia, they account for more than 75% of the etiologies of this cancer. The purpose of this study was to compare the clinical features and survival in patients with Hepatitis B Virus-related Hepatocellular Carcinoma (HBV-HCC) and Hepatitis C Virus-related Hepatocellular Carcinoma (HCV-HCC).

Patients and Methods: A retrospective study (January 2002-December 2017) including all cases of HCC developed on post viral B and C cirrhosis, diagnosed in Gastroenterology department of Habib Thameur hospital was conducted. Epidemiological, clinical, biological, morphological characteristics, therapeutic modalities and evolution were compared between HBC and HCV related HCC.

Results: A total of 84 cases of HCC were included: 53 patients with HCV-HCC and 31 patients with HBV-HCC. The mean age of HBV-HCC patients was 60.1 years, while it was 68.9 years in HCV-HCC patients (p=0.03). The male/female ratio was 9.3 in HBV-HCC, while it was 1.4 in HCV-HCC (p<0.001). The mean alpha-fetoprotein level in HBV-HCC was 16196ng/ml, while it was 28148ng/mL in HCV-HCC (p=NS). The mean tumor size was 50.1mm in HBV-HCC, while it was 44.5mm in HCV-HCC (p=NS). According to the BCLC classification, patients with HBV-HCC were classified in stage A in 6.4% of cases (N=2), in stage B in 22.5% of cases (N=7), in stage C in 38.7% of cases (N=12) and stage D in 32.2% of cases (N=10). Patients with HCV-HCC were classified in stage A in 26.4% of cases (N=14), in stage B in 30.1% of cases (N=16), in stage C in 20.7% of cases (N=11) and stage D in 22.6% of cases (N=12) (p=0.05).The mean survival was 8,6 months in HBV-HCC, while it was 23.9 months in HCV-HCC (p=0.03).

Conclusion: Compared with HBV-HCC patients, HCV-HCC patients were older, had a lower male/female ratio, were diagnosed at a less advanced stage and had a better survival.

Keywords: Hepatocellular Carcinoma; Cirrhosis; Viral Hepatitis; Prognosis

Introduction

Hepatocellular Carcinoma (HCC) is actually the sixth most frequent cancer [1] accounting for 6% of all newly diagnosed cancer cases worldwide [2]. Chronic hepatitis B and C remain the main causes of cirrhosis and therefore hepatocellular carcinoma in Africa and South East Asia [3]. In Tunisia, they account for more than 75% of the etiologies of this cancer.

Several studies have focused on comparing the clinical, morphological, therapeutic and evolutionary aspects between hepatitis B and C-related HCCs and those not linked to these viruses (secondary to immunological cirrhosis, alcoholic or non-alcoholic steatohepatitis). Most of them concluded that hepatitis B and C related HCCs had a poorer prognosis. However, few studies have focused on the impact of the viral etiology (B or C) of cirrhosis on clinical presentation and outcome of HCC.

The aims of our study were to:

Compare, according to the type of the virus, the clinical, morphological, therapeutic and evolutionary characteristics of HCC.

Determine the impact of the virus type on survival during HCC

Patients and Methods

Study population

A 16-years long, single-center, retrospective study (January 2002-December 2017) including all HCC complicated post viral B or C cirrhosis hospitalized in the department of Gastroenterology of Habib Thameur Hospital was conducted.

Inclusion criteria

The diagnosis of cirrhosis was either confirmed by histology or retained on a cluster of arguments: clinical, biological, endoscopic

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and radiological.

The diagnosis of HCC was retained according to the evolution of the international recommendations according to the Barcelona criteria of 2000 then on the criteria of the European association of the study of liver (EASL) of 2012.

The diagnosis of the viral etiology of cirrhosis was classified post viral if anti-HCV antibodies and/or viral load (HCV RNA) were isolated and post viral B if the presence of serum HBsAg. And/or a viral load (HBV DNA) positive was observed.

Non-inclusion criteria

Patients were not included if HCC occurred

on healthy liver

on non-cirrhotic chronic post-viral B or C hepatopathy

on cirrhosis of undetermined etiology

Exclusion criteria

Patients with:

HBV + HCV infection

HBV or HCV + HIV infection

HBV + HVD co-infection

Excessive and chronic consumption of alcohol

Data collection

For each patient, the following information were collected

Clinical data: Age, sex, Family history of chronic liver disease and post viral cirrhosis, Habits (Tobacco, alcohol), duration of cirrhosis (if previously known), Possible anti-viral treatment received, Circumstances of discovery of HCC, clinical examination (OMS performance status, body mass index, signs of portal hypertension and hepatocellular insufficiency, liver examination) as well as biological examination (complete liver tests, prothrombin rate, electrophoresis of proteins, renal function and alpha-fetoprotein).

Portal hypertension endoscopic signs as well as morphological characteristics of HCC were also noted. Extension and classification according to Milan criteria and Barcelona Clinic Liver Cancer Group (BCLC) Classification was assessed. Child Pugh score was calculated.

Therapeutic indications and modalities and evolution (duration of follow up, complications of treatment, RESICT criteria, and survival) were specified

Statistical analysis

Statistical analysis was performed by SPSS 20.0 software. Qualitative variables were compared by the Khi 2 test and quantitative variables by the student test. A p value was considered as statistically significant if lower than 0.05. Survival analysis was performed by Kaplan-Meier method.

Results

During the study period, 84 patients with HCC occurring on viral cirrhosis were included. There were 53 (63%) post viral C cirrhosis and 31 (or 37%) post viral B cirrhosis.

Table 1: Comparison of clinical characteristics according to the etiology of cirrhosis.

Clinical characteristic	G1 : Hepatitis B cirrhosis	G2 : Hepatitis C cirrhosis	p
Hepatomegaly	90.3% (28/31)	83%(44/53)	NS
Splenomegaly	77.4%(24/31)	67.9%(36/53)	NS
Collateral circulation	51.6%(16/31)	45.2%(24/53)	NS
Ascitis	48.3%(15/31)	41.5%(22/53)	NS
Lower limb oesdema	35.4%(11/31)	26.4%(14/53)	NS
Jaundice	45.1%(14/31)	35.8%(19/53)	NS

Table 2: Comparison of biological parameters according to the etiology of cirrhosis.

Biological parameter	G1 : Hepatitis B cirrhosis	G2 : Hepatitis C cirrhosis	p
Prothrombin time (%)	60.7%(32%-82%)	64.4%(34%-96%)	NS
ASAT (UI)	114.1(25-416)	88.6(23-430)	NS
ALAT (UI)	61.1(22-172)	51.7(12-240)	NS
Alkaline phosphatase (UI)	220.1(90-650)	199.2(61-750)	NS
GGT (UI)	104.3(23-372)	106.2(18-720)	NS
Bilirubin (µmol)	54.1(18-298)	45.4(11-515)	NS
Albumin (g/l)	27.4(21-35)	28.9(20-36)	NS

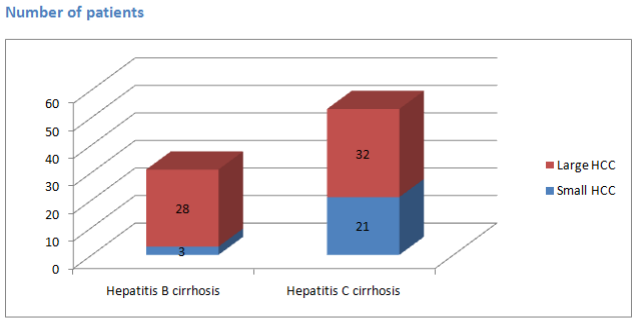

Figure 1: Comparison of MILAN criteria according to the etiology of cirrhosis.

Sex ratio was 1.4 (49 men and 35 women). For the group of patients with post-hepatitis B HCC, the sex ratio was 9.33 (28 males/3 females) while for the group of patients with post hepatitis C HCC, the sex ratio was 0.65 (21 men/32 women). The sex difference between the 2 groups was statistically significant ($p < 0.001$).

Mean age at diagnosis of HCC was 65.7 years [43-90 years]. For HCV-related CHC cases, mean age was 68.9 years [43-81 years] while for other CHC cases that were HBV-related, the mean age was 60.1 year [51 to 90 years]. The age difference between the two groups was statistically significant ($p = 0.03$).

The most frequent personal history observed was high blood pressure (43% for HCV-related HCC vs. 22.5% for the HBV related HCC with a p value of 0.05), diabetes (22.3% vs. 25.2%) and cholecystectomy (18.8% vs 6.4%).

The discovery of HCC was concomitant with the diagnosis of cirrhosis in 45.1% (n=14) cases of HBV and in 62.2% (n=33) cases of HCV without statistically significant difference between the two groups.

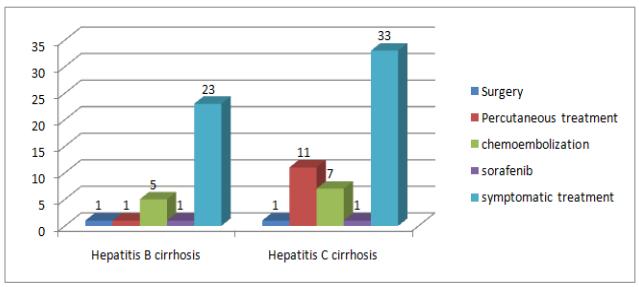

Figure 2: Comparison of therapeutic modalities according to the etiology of cirrhosis.

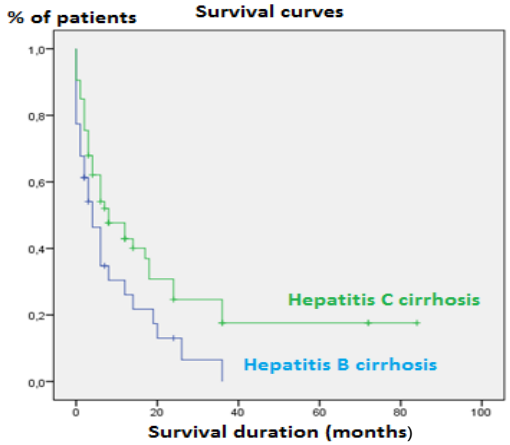

Figure 3: Survival curves according to the etiology of cirrhosis.

HCC was found in routine screening in 12 of the 14 known cirrhotic B patients (85.7%) and in 27 of 33 known cirrhotic C patients (81.1%), or 50.9% of this group of patients.

The other revealing symptoms (right hypochondirum pain with loss of weigh, variceal bleeding or decompensation of the cirrhosis) were similar between the two groups.

At the time of diagnosis of HCC, the different physical and biological examination abnormalities in the 2 groups of patients were similar between the two groups and summarized in Tables 1 and 2.

Alpha-fetoprotein was measured in 24 HBV cirrhotic patients (77.4%) and as high in 79.1% (N=19) of patients. Regarding the other group of HCV cirrhotic patients, AFP was dosed in 44 patients (83%) and was high in 90.9% (N=40) of patients. Comparing AFP levels between two groups, there was no statistically significant difference.

The comparison between the 2 groups concerning morphological characteristics of HCC (number, size and localization) showed no statistical differences between the two groups.

A portal vein thrombosis was noted in 13 HBV cirrhotic patients (41.9% of cases) and 12 HCV cirrhotic patients (22.6% of cases) with a statistically significant difference between 2 groups (p=0.05).

At the time of diagnosis, three cirrhotic C patients (5.6% of cases) and two cirrhotic B patients (6.4%) had metastases (in the lung, bone or surrenal).

The distribution of the two groups according to the Milan criteria is resumed in Figure 1. The difference between the 2 groups of patients according to the Milan classification was statistically significant (p = 0.008).

Concerning Child Pugh classification, for the HBV related HCC, cirrhosis was classified as ChIld Pugh A, B and C respectively in 8 (25.8%), 17 (54.8%) and 6 (19.3%) patients. For the other group, cirrhosis was classified Child A in 41.5% of cases (N=22), Child B in 39.6% of cases (N=21) and Child C in 18.8% of cases (N=10). The difference between the 2 groups was not statistically significant.

Upper endoscopy was performed in all HVC cirrhotic patients and thirty patients (96.7% of cases) HBV cirrhotic patients. Endoscopic signs of postal hypertension (oesophageal varices, gastric varices and/or portal gastropathy) were found in 80% (N=24) of HBV related HCC and 90.5% (N=48) of HCV related HCC without any statistically significant difference.

The difference between the 2 groups concerning performance status was also not statistically significant.

According to the BCLC classification, HVB related HCC were classified in stage A in 6.4% (n=2), in stage B in 22.5% (n=7), in stage C in 38, 7% (n=12) and stage D in 32.2% (n=10).

HCV related HCC were classified stage A in 26.4% (n=14), stage B in 30.1% (n = 16), stage C in 20.7% (n=11) and stage D in 22.6% (n=12). The difference between the 2 groups was statistically significant (p=0.05).

A curative treatment was proposed for 2 HBV related HCC (6.4%) and 12 HCV related HCC (22.6%) with a statistically significant difference (p=0.05).

Palliative treatment with intra-arterial chemoembolization was indicated for 7 patients with HCV related HCC (13.2% of cases) and 5 patients with HBV related HCC (16.7%). Systemic treatment with sorafenib was indicated in one patient for both groups.

For the rest of the patients (33 HCV cirrhotic patients and 23 HBV cirrhotic patients), only a symptomatic treatment was proposed. Therapeutic indications are summarized in Figure 2.

There was no significant difference between the two groups regarding treatment response and post-treatment complications.

The mean survival of HCC occurring on post viral cirrhosis was 17.9 months. It was respectively 8.6 months and 23.1 months in HBV and HCV related HCC. The difference between the 2 groups was statistically significant (p=0.03) (Figure 3).

Discussion

Hepatocellular carcinoma is currently the sixth most common cancer and the third leading cause of cancer deaths in the world [1]. Its incidence continues to increase throughout the mode, estimated between 700 000 and 800 000 new cases per year [4] with however unequal geographic distribution with high incidence areas such as sub-Saharan Africa and south-west Asia and low incidence areas such as Western Europe and the United States [4,5].

This geographical disparity is essentially linked to a different distribution of the etiological factors of HCC:

Hepatitis B virus and exposure to Aflatoxin in Africa and Asia

Hepatitis C virus and alcohol consumption in Europe and the United States

Despite the therapeutic advances in recent decades, it remains a cancer of very poor prognosis. In Tunisia, post-viral cirrhosis (B and C) are the main pre-neoplastic conditions predisposing to this type of cancer.

Tunisia is one of the low incidence countries of HCC (estimated incidence of 1.49 new cases/100000 inhabitants according to GLOBOCAN 2012) [6].

Viral hepatitis (B and C) remains the most common cause of hepatocellular carcinoma in our country.

Thirty percent (30%) of cirrhotic patients (all causes) will develop CHC during the course of evolution, with an estimated incidence of between 1% and 8% per year [4].

This risk of degeneration is not the same for all patients and depends mainly on the etiology of cirrhosis with a higher risk in case of viral cirrhosis (3% to 8%).

By analyzing the results of our series, and despite being a country with low HCV endemicity and HBV intermediate endemicity, the most common viral cause of HCC in Tunisia remains cirrhosis due to chronic hepatitis C. This is partly explained by the significant frequency of transition to chronicity and cirrhosis in case of HCV infection compared with chronic portage of HBV.

The age of onset obviously varies according to the viral etiology of cirrhosis. It is earlier in populations with a high incidence of HCC and in cases of HBV cirrhosis [4].

In our series, for HCV-related CHC cases, the mean age was 68.9 years [43-81] while for HBV related HCC, the mean age was 60.1 years [51-90] The age difference between the two groups was statistically significant (p=0.03).

CHC on HBV cirrhosis affects men more frequently by comparing it with those developing on post HCV cirrhosis. This disparity in occurrence by sex is largely confirmed by several Asian [7,8] and Western studies [9] and may be explained in part by the mode of viral transmission with a high frequency of sexual transmission of HBV in men and parenteral transmission (transfusions, tattoos and scarifications) of HCV in women in our country.

In our study, for the group of patients with HBV related HCC, the sex ratio was 9.33 while for the other group of patients with HVC related HCC, the sex ratio was 0.65 with a statistically significant difference ($p < 0.001$).

The diagnosis of HCC on post viral cirrhosis (B or C) in our country is usually performed at a late stage when the disease is clinically manifest [10].

In our series, HCC was however discovered in routine screening in 12 of the 14 HBV cirrhotic patients (85.7%), and in 27 of the 33 HCV cirrhotic patients (81.1%). The difference between the 2 groups was not statistically significant.

These data concerning the circumstances of HCC discovery on post viral cirrhosis B in our country encourage us to further improve our behaviors in current practice in screening for HCC [11,12].

The main one being a better sensitization of cirrhotic patients of the interest of following an adequate screening program by a six-monthly ultrasound thus allowing the discovery of HCC at an early stage eligible for curative treatment [13].

In our series and according to the BCLC classification, HBV cirrhotic patients were however frequently diagnosed at advanced stage. Indeed, they were classified in stage A in 6.4% of cases (n=2), in stage B in 22.5% of cases (n=7), in stage C in 38.7% of cases (n=12) and stage D in 32.2% of cases (n=10).

HCV cirrhotic patients were classified in stage A in 26.4% of cases (n=14), in stage B in 30.1% of cases (n=16), in stage C in 20.7% of cases (n=11) and stage D in 22.6% of cases (n=12). The difference between the 2 groups of patients was statistically significant (p=0.05). This could explain that HCV related HCC were more likely to have access to a curative treatment compared to HVB related HCC. This also explains the better survival who was respectively 8.6 months and 23.1 months in HBV and HCV related HCC with a statistically significant difference (p=0.03).

Conclusion

According to our study, hepatitis C virus was the most common viral etiology of HCC (responsible of more than 60% of cases).

The results of our study are consistent with the results of several, mostly Asian, published studies that focus on the impact of viral etiology of cirrhosis on the clinical presentation and evolution of HCC. Indeed, viral cirrhosis related HCC is considered to have a poor prognosis, but it seems that the HBV-related HCC has some peculiarities that distinguish it from the one related to HCV because it occurs at a younger age, with a more advanced stage and a lower survival.

Our study lead us to insist on few points to improve the prognosis of viral cirrhosis related HCC:

Vaccination against HBV in at-risk populations: health professionals, HBsAg patient's sexual partners.

Treatment of chronic post viral hepatopathies before the stage of cirrhosis with a special mention for post viral hepatitis C direct antiviral drugs they allow a sustained virological response in more than 90% of cases.

Strengthening screening programs by experienced sonographers. This screening will allow an early stage diagnosis, thus, increasing the chances of accessing curative treatment and improving therefore survival.

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