Influence of hepatitis viruses on clinico-pathological profiles and long-term outcome in patients undergoing surgery for hepatocellular carcinoma

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BACKGROUND: **The global risk of hepatocellular carcinoma (HCC) is largely due to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. In recent years, however, an increased prevalence of non-viral HCC has been noted. The clinical impact of the presence/absence of viral infections in HCC remains controversial. The present study aimed to assess the effect of hepatitis viruses on demographics, clinical and pathological features and long-term outcome in a large cohort of Romanian patients who underwent surgery for HCC.**

METHODS: **The study included 404 patients with HCC who had undergone resection, transplantation or radiofrequency ablation at a single institution between 2001 and 2010. The patients were divided into four groups: 85 patients with hepatitis B virus infection (HBV group), 164 patients with hepatitis C virus infection (HCV group), 39 patients with hepatitis B and C virus co-infection (HBCV group), and 116 patients without viral infection (non-BC group).**

RESULTS: **The patients of both HBV (56.0±11.3 years) and HBCV groups (56.0±9.9 years) were significantly younger than those of the HCV (61.0±8.5 years, *P*=0.001) and non-BC groups (61.0±13.0 years, *P*=0.002). Interestingly, the prevalence of liver cirrhosis was significantly lower in the non-BC group (47%) than in any other subsets (72%-90%, *P*<0.002). Furthermore, the non-BC patients were more advanced according to the Barcelona Clinic Liver Cancer stages than the patients of the HCV or HBCV groups (*P*<0.020); accordingly, they were more frequently assessed beyond the Milan criteria than any other groups (*P*=0.001). No significant differences in the disease-free or overall survival rates were observed among these groups.**

CONCLUSIONS: **Patients with non-viral HCC are diagnosed at advanced ages and stages, a situation plausibly due to the poor effectiveness of cancer surveillance in community practice. The presence of viral infections does not appear to impair the long-term prognosis after surgical treatment in patients with HCC; however, there is a trend for worse disease-free survival rates in HBCV patients, though statistical significance was not reached.**

(***Hepatobiliary Pancreat Dis Int 2014;13:162-172***)

KEY WORDS: **hepatitis B virus; hepatitis C virus; hepatocellular carcinoma; recurrence; prognosis**

Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the third leading cause of cancer-related death worldwide.[1] Thus, HCC is not only common but also very deadly, with a 5-year survival rate of less than 10%.[2] According to the age-adjusted HCC incidence per 100 000 habitants, different areas are classified as low (<5), intermediate (5-15) and high (>15).[3] Romania is considered to be at an intermediate incidence (8 HCC/100 000 habitants).[4]

For the past century, the global risk of HCC was largely due to hepatitis B virus (HBV) and hepatitis

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doi: 10.1016/S1499-3872(14)60026-6

C virus (HCV) infections, along with aflatoxin intoxication, excessive alcohol consumption, obesity and diabetes.[5, 6] Furthermore, diabetes mellitus has a negative impact on both overall and disease-free survival after curative-intent treatments for HCC.[7] Chronic hepatitis B and C, mostly in the cirrhotic stage, are responsible for the great majority of cases of HCC worldwide,[8] as appears to be the case in Romania.[4, 9] Co-infection with both viruses is often noticed in HCC patients due to their similar ways of transmission; this situation has significantly impacted the overall burden of chronic liver disease.[10] HBV and HCV co-infection is associated with more severe forms of liver disease compared with chronic hepatitis caused by a single virus.[11] At the molecular level, distinct chromosomal abnormality patterns and transcriptomic signatures were observed in HCC without viral infection.[12, 13] Therefore, there should be some clinico-pathological differences between HCC in patients without viral infection and those associated with hepatitis viruses.

With regards to its natural history and its clinical presentation, HCC is a heterogeneous disease. The incidence of HCC varies across the world due to geographic differences in the prevalence of risk factors.[14] Furthermore, in addition to different etiology rates, other significant differences among countries are commonly noticed regarding patient age, gender ratio, tumor size or degree of underlying liver damage.[15] Nevertheless, biological characteristics appear to affect the natural history of HCC.[16]

Curative-intent treatment options for HCC include liver resection, liver transplantation and ablative therapy, depending on the tumor stage and functional status of the liver.[17-20] However, despite the above-mentioned heterogeneity, no differences regarding long-term survival were observed between Western and Eastern centers when adjusted for clinico-pathological factors.[15] Early detection and curative resection are considered the most important factors for long-term outcome.[21] The effect of HBV and HCV infection on clinico-pathological features and long-term outcome in HCC-treated patients has been previously studied; however, most of these studies are from Eastern Asia.[22] In Eastern Europe there is a conspicuous paucity of reports regarding the epidemiology[23-25] and surgical management[17, 26] of HCC. Furthermore, none of the works published thus far have addressed the effect of hepatitis on long-term prognosis. We assessed the potential differences determined by the presence of HBV or HCV in a large cohort of HCC patients from a single surgical center of an Eastern European country. Only patients who were surgically treated with liver resection, liver transplantation or radiofrequency ablation were considered.

Methods

Patients

The data from 404 patients who had been treated from January 2001 to November 2010 with a final pathological diagnosis of HCC were retrospectively reviewed from a prospective-gathered electronic database established at the Center of General Surgery and Liver Transplant from the Fundeni Clinical Institute (Bucharest, Romania). Only patients who underwent surgical treatment (i.e., liver resection, liver transplantation or radiofrequency ablation) were considered. Informed consent was obtained from each patient, and the study was approved by the Local Ethics Committee.

The preoperative work-up included a serologic examination for HBV (hepatitis B surface antigen) and HCV (hepatitis C antibody) for all patients. The serum tumor marker alpha-fetoprotein (AFP) was preoperatively assessed in 207 patients (51%); the cut-off value was <32 ng/dL. Computed tomography (CT) and/or magnetic resonance imaging (MRI) examinations were performed to evaluate the extent of the disease, tumor location and characteristics. For patients who underwent ablation, the size and number of tumors were noted with imaging examinations and the tumor type was established through biopsy (patients without a positive biopsy for HCC were excluded). The choice of treatment modality was performed according to the patient status [Child-Pugh score or Barcelona Clinic Liver Cancer (BCLC) classification] and tumor features (localization, size, number and stage).

The patients with HCC were divided into four groups: 85 patients with only hepatitis B virus infection (HBV group), 164 patients with only hepatitis C virus infection (HCV group), 39 patients with hepatitis B and C virus infection (HBCV group), and 116 patients with no viral infection (non-BC group). The comparative analyses included demographics (age, gender and residence), serum AFP level, Child-Pugh score, staging systems such as Okuda, BCLC, the Cancer of the Liver Italian Program (CLIP), Milan criteria, type of treatment, pathology data (number and size of the tumors, underlying liver cirrhosis, Edmonson-Steiner grading system), disease-free and overall survival rates.

The follow-up protocol included clinical examination, serum AFP level and ultrasound and/or CT and/or MRI every 3 months in the first year and every 6 months thereafter. Data for AFP were available for 48 patients in the HBV group (56%), 90 patients in