Hepatocellular carcinoma: Ten years experience among veterans in Puerto Rico

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Purpose: The aim of our study is to determine the characteristics of hepatocellular carcinoma (HCC) as well as risk factors, demographics, survival rates and the use of diagnostic and therapeutic modalities among veteran patients in Puerto Rico.

Methods: A retrospective study of 114 patients with Hispanic background and biopsy-proven HCC diagnosed at the VA Caribbean Healthcare System from 1992 to 2002 was performed. Demographics data, Child-Turcotte-Pugh (CTP) score, presence of cirrhosis, viral serology, alcohol and/or other liver diseases history, diagnostic modalities, lesion size, therapy, and overall survival were examined.

Results: The mean age was 66.6 years old. 82% had known underlying cirrhosis. 60% had alcoholic liver disease (ALD), 33% positive serology for hepatitis C (HCV) and 21% both. 5.3% had chronic hepatitis B virus (HBV) infection. Additional causes were not present. CTP classification was: A (42%), B (44%) and C (14%). Abdominal CT scan demonstrated most of the lesions, while ultrasound only 57%. Alfa-fetoprotein was diagnostic in 32%. Mean survival was 10.3 months, better for those with CTP score A. Only 42% of the patients received any kind of therapy.

Conclusions: ALD is the principal underlying liver disease in our HCC patients, closely followed by chronic HCV infection. Less than half of our patients received treatment mainly due to advanced disease for which the over survival was less than a year. HCC continues to be a dreadful disease with poor prognosis for which aggressive screening should be considered for all patients with cirrhosis and advanced liver disease regardless of the cause.

Key words: Hepatocellular carcinoma, Veterans.

Hepatocellular carcinoma (HCC) is a common and important cancer and is associated with a poor prognosis and outcome. It accounts for approximately 6% of all human cancers (1,2). Approximately half million cases occur annually worldwide, making HCC the fifth most common malignancy in men and the ninth in women. Eighty percent of the cases arise in the sub-Saharan Africa and Southeast Asia (3). In the United States, the incidence of HCC has been increasing over the past twenty years in part due to the hepatitis C virus (HCV) epidemic (1,4).

More than 80% of HCC cases occurs in individuals with cirrhosis of the liver (5). The annual incidence of HCC in cirrhotic patients is 1-6% (6). The major risk factors for HCC include chronic hepatitis B virus (HBV) and/or HCV infection, hereditary hemochromatosis (HH), primary biliary cirrhosis (PBC) and cirrhosis secondary to alcohol liver disease (ALD) (7). Rare cases of HCC related to cirrhosis secondary to Wilson's disease (WD) and alpha-1 anti-trypsin deficiency have been reported. Aflatoxin exposure is a common risk factor in south-East Asia and Africa and hereditary tyrosinemia in patients less than 2 years old.

The age-adjusted incidence of primary liver cancer in men in Puerto Rico is 4 per 100,000 persons based on a recent publication which includes the incidence rates from 24 geographical regions around the world (8-10). It is similar to the age-adjusted incidence rates in whites in USA (3 per 100,000) but less when compared to other areas such as Osaka, Japan (47 per 100,000), Hong Kong (36 per 100,000), Shangai, China (22 per 100,000), Varese, Italy (13 per 100,000) and blacks in USA (7 per 100,000). It is important to mention that although this publication takes into account all primary liver cancers, in most of

these countries HCC accounts for 70% to 85% of them (10). A previous article from the Puerto Rico Cancer Registry showed that 75 new cases of primary carcinoma of the liver were reported in 1982, for an adjusted incidence rate of 1.8 per 100,000 persons (11).

Our aim was to determine the characteristics of HCC among Hispanic veterans at the San Juan VA Medical Center. Besides determining risk factors in our population, we were interested in obtaining information regarding demographics, survival rates and the use of different diagnostic and therapeutic modalities among veteran patients in Puerto Rico.

Materials & Methods

This retrospective study involved the evaluation of the medical records of 114 patients with histological confirmation of HCC during the period of January 1, 1992 to December 31, 2002 at the VA Caribbean Healthcare System, a 375 bed, tertiary hospital which offers care to patients from Puerto Rico and the U.S. Virgin Islands.

The following parameters were retrospectively analyzed based on the data obtained from the medical records: gender, age, ethnic background, presence or absence of cirrhosis, risk factors for HCC, Child-Turcotte-Pugh (CTP) classification, macroscopic features, lesion size, staging (using Okuda staging classification), utilization and results of abdominal CT scan and/or ultrasound, serum alpha-fetoprotein (AFP) level, therapeutic modalities used and overall survival.

Cirrhosis was determined by either histopathology or by the presence of signs of portal hypertension by laboratory data, imaging or endoscopic studies. Diagnosis of chronic HBV or HCV was established by the presence of positive serology for HBsAg or anti-HCV antibodies respectively. ALD was considered a risk factor if there was documentation on the medical record of "heavy alcohol intake", which was defined as consumption of > 50 g/day.[10] The diagnosis of autoimmune hepatitis (AIH) or PBC was considered if there was evidence of significant elevation of the ANA test, hypergammaglobulinemia, histological confirmation, or documentation of the diagnosis on the record on the former, or by the presence of anti-mitochondrial antibodies (AMA) on the later. WD, HH, alpha 1 antitrypsin deficiency were considered risk factors only if there was documentation of the diagnosis on the medical record of the patient. Laboratory data was not used to establish a diagnosis based in the fact that iron, total iron binding capacity, ferritin level or ceruloplasmin levels can be altered by the presence of cirrhosis of any etiology.

In patients with cirrhosis, CTP score was obtained if

there was documentation of serum albumin and bilirubin levels, coagulation parameters, presence and degree of ascites and hepatic encephalopathy. Data was obtained from the date closest to the histological diagnosis. Okuda stage was calculated taking into account the following parameters: tumor size, presence or absence of ascites and bilirubin level (12).

Alpha-fetoprotein level was considered to be normal if there was a value <10 ng/dL, abnormally elevated but not diagnostic if the values were >11 but <400 ng/dL, and diagnostic if the values were of 400 ng/dL or more.

Results of imaging studies including abdominal U/S and abdominal/ liver CT scan were reviewed to obtain information regarding size and morphology of the lesion (s). If more than one imaging study was available, the one with the closest date to the day of the biopsy was chosen to provide the information. An imaging study was considered positive if a mass with characteristics of HCC was reported.

Overall survival was defined as the time in months between histological confirmation of diagnosis, and date of death, or last documented encounter.

Statistical Analysis

Data was analyzed using the Students t- and chi- square test, and is presented as mean. A p value of <0.05 was considered to indicate statistical significance.

Results

All one hundred fourteen patients (100%) were men of Hispanic background The mean age was 66.1 years-old. There was evidence of underlying cirrhosis in 93 patients (81.5%). (Table 1) Regarding the stage of cirrhosis, 39 (42 %) cases were CTP class A, 41 (44%) class B, and 13 (14%) were class C. (Figure 1)

Risk factors for HCC were known in 97 (85%) of the cases. Forty-seven (41%) of the patients had history of ALD, 19 (17%) had evidence of infection with HCV, 25 (22%) had concomitant HCV and ALD, 5 (4%) had concomitant chronic HBV infection and ALD, 17 (15%) had no identified risk factors and 1 (1%) had concomitant chronic HBV, HCV and ALD. (Figure 2) There was no anti-HCV serology available in 22 (21%) of the cases.

A solitary lesion was the dominant presentation, closely followed by the multifocal pattern. Liver lesions were: solitary in 43%, paucifocal (2 or 3 nodules) in 14%, multifocal (> 3 nodules) in 36.8% and diffuse in 6.2%. Most of the patients (67%) had lesion (s) which measured more than 5 cm. According to the Okuda classification, more than half of the patients were stage II or III (stage I 37.7%,

stage II 46.5 % and stage III 15.8%) at the time of the diagnosis (Table 2).

Serum AFP levels were available in 104 cases. Only 33 (32%) cases had a serum AFP level which was considered diagnostic (>400 ng/mL) and 16 cases had a normal serum AFP, despite having histologicaly proven HCC. In the great majority of cases (53%) the serum AFP was abnormally elevated but not diagnostic (Figure 2).

The two main imaging modalities used for the diagnosis of HCC were abdominal ultrasound (U/S) and Abdominal/ Liver CT scan. Fifty seven patients had an ultrasound performed; of these only 33 (57%) had findings suggestive of the presence of HCC. On the other hand, 114 patient had an abdominal/liver CT scan done which was able to reveal findings suggestive of HCC in 109 (95.6%) of the cases (Figure 3). In the cases in which the CT scan did not reveal the presence of HCC, other imaging studies such as liver magnetic resonance imaging (MRI) or gallium studies were used to identify the liver lesion.

Only 42% of the cases received some kind of treatment. Only a minority underwent potentially curative intervention, such as surgical resection (6 cases) or liver transplantation (2 cases). The great majority received palliative treatment. The therapy provided consisted of: systemic chemotherapy (SC) in 22 cases, trans- arterial chemoembolizaion (TACE) in 14 cases and percutaneous ethanol injection (PEIT) in 7 cases (Figure 4).

The overall survival was similar despite different underlying risk factors. Patients with HCV infection and ALD had a mean survival of 12.6 months respectively; while those with concomitant HCV and ALD had a lower mean survival of 10.1 months. This difference was not statistically significant. Survival time varied depending on the underlying CTP score. Patients with compensated cirrhosis (CTP A) at the time of diagnosis had a mean survival of 18.9 months, while the mean survival for CTP class B was 8.8 and 7.6 months for those with CTP C. There was no statistically significant difference among these values (Figure 5).

Discussion

For the past two decades, there has not been any published data regarding the characteristics of hepatocellular carcinoma in Puerto Rico (11). This study is the first to address this issue and analyses a subset of Hispanic veterans patients that receive care at the VA Caribbean Healthcare System.

The main risk factor for HCC in our veteran population was ALD, followed closely by chronic HCV. There are some important points to make regarding this finding. First, the true prevalence of HCV in our population may probably be underestimated since approximately 22% of the patients were not tested for HCV infection. Most of these patients had HCC diagnosed between 1993 and 1995, closely after the identification of HCV as the etiologic agent of what was previously known as non A non B hepatitis. We may expect in the future an increase of HCV-related HCC as has occurred in the United States over the last 20 years (13). Another important fact is that at least 27% of the patients in our study had concomitant ALD and chronic viral infection. It has been shown in other studies that alcohol acts synergistically with viral hepatitis in increasing the risk of HCC.

We were not able to identify a risk factor or underlying cause for chronic liver disease (CLD) and HCC in 15% of the cases. This number is similar to other published series in the United States in which 15% to 50% have none of the known causal factors (10). Several studies have suggested a relationship and possible increased risk of HCC in patients with diabetes mellitus (DM), obesity and/or non-alcoholic fatty liver disease/ non-alcoholic steato-hepatitis (NAFLD/NASH) (1,14). In the general population of Puerto Rico the prevalence of type 2 DM has been shown to be 9.67% which is superior to that observed in the United States (5.6%) (15). Data from a study performed in our institution found an incidence of 32% of DM among patients with HCV (15). In this study we did not look at the relationship of these factors to HCC, for which further analysis of such factors deserves investigation.

In order to detect HCC as early as possible, monitoring cirrhotic patients with serial ultrasound or CT-scan and serum AFP has become a common practice. The rationale is to detect small asymptomatic HCC nodules in which early therapy may be offered, however so far no study has shown that this translates into decreased mortality (16). The two main imaging modalities used in our institution for HCC surveillance are abdominal U/S or Liver CT scan. In our study, 57 patients underwent an abdominal U/S during their evaluation, but in only in 33 (57%) patients the study was suggestive of HCC. Previous studies has reported that U/S has a sensitivity of 60%, specificity of 90% and a positive predictive value of 70%. A possible explanation for this difference is that abdominal ultrasound is highly operator dependant, there is great variation in the experience among examiners and there may be differences in the specific techniques used at each institution. On the other hand, all the patients in our study had a CT scan as part of the evaluation. The study showed findings suggestive of HCC in 109 (95.6%) patients, demonstrating its superiority when compared to ultrasound. Helical CT allows the detection and characterization of most hepatic masses more than 2 cm in diameter (17). The use of Helical CT scan as a screening

tool for HCC is increasing, either as the mainstay imaging study among cirrhotic patients or as in some centers, alternating with ultrasound (17).

Despite the fact that 85% of our patients with documented AFP levels had above-normal serum AFP levels, only 32% had a value that was considered diagnostic. This compares to previous published data in which positive predictive values between 9%-32% has been shown to limit its usefulness (1). An important comment to make is that in patients with abnormally elevated AFP and normal U/S or CT scan, further evaluation with other cross sectional studies such as dynamic gadolinium MRI should be considered (1,17). AFP has limitations in its function as a diagnostic tools, but probably is the only tumor marker that is widely available. Other markers, such as Glypican-3 will probably emerge as a diagnostic alternative in a near future (1).

In our study, the great majority of patients were diagnosed with HCC at an advanced stage. As described above the average age at diagnosis was 66.1 years old. In the great majority of patients (83.5%) there was evidence of underlying cirrhosis which was advanced (either CTP B or C) in more than half of the patients. Is also noted that at the moment of the diagnosis it was common to observe paucifocal, multifocal or a diffuse tumors, while only 43% of the cases presented with a solitary lesion. Sixty seven percent of the patients also presented with a large diameter lesion (>5 cm) at the moment of the diagnosis.

The Okuda classification is one of the different systems that has been proposed as a staging tool for HCC. Data from a Canadian study which included 257 patients demonstrated difference in survival among the different stages, with a median survival of 36.3 months, 7.0 months and 3.5 months for Okuda stage I, II, III respecevely (12). A large proportion of the cases in our study (62.3%) were either in stage II or III at the moment if diagnosis which is also evidence of the advance stage of the disease.

Regarding the experience with different therapeutic modalities available at our institution there are few important points to discuss. Our data showed that only 42% of the patients were candidates for any kind of therapy. The great majority underwent only palliative therapy such as systemic chemotherapy or hormonal therapy which in general is of limited value (18). Only a minority of the patients in our series underwent surgical resection or liver transplant, which are the only techniques which can offer a cure for the disease. The fact that many of our patients had advanced underlying cirrhosis deemed most of them unsuitable candidates for a surgical resection of the tumor. Liver transplant is probably the treatment of choice in cirrhotic patients with early-stage HCC, but unfortunately many still die waiting for a transplant (19). There has been

major improvement in the survival among patients who undergo liver transplant due to HCC. Actually the survival rate at 4 years is 75% which is not different from the expected survival among non-HCC cases. The current enrollment criteria used by many transplant centers is having a single tumor <5 cm or no more than 3 tumors all < 3 cm on preoperative imaging studies. The great majority of the patients in our study did not meet these criteria, reason why OLT was not a viable option. Although age is a relative contraindication, some of the centers have a cut-off at age 65, for considering for OLT evaluation. This also may have influenced the candidacy of some of our patients for this type of procedure.

Percutaneous ethanol ingestion (PEI) and trans-catheter artery chemoembolization are techniques which are used in selected cases to downgrade the tumor or as bridging therapy before a definite treatment. PEI has better outcomes in single or multiple small lesions, and TAC has shown to offer some improvement in survival (18). The efficacy of these two techniques has been shown to be related to tumor size and Child Pugh score, explaining why they were used in selected cases among our population.

In our opinion, advanced HCC at the moment of the diagnosis, and poor candidacy for curative therapy are likely responsible for the poor survival observed in our population. The overall survival among patients with HCV and ALD was similar with an average survival of 12.6 months. Although we would have expected a decrease in survival among patients with synergistic factors such as concomitant ALD and HCV, our data showed a decrease in the mean survival (10.1 months) which was no statistically different. Despite differences in the average survival of patients with compensated cirrhosis, there was no statistical significance between groups.

Conclusions

Our study provides important and updated information about the characteristics of Hispanic patients with HCC in Puerto Rico. Although ALD is the principal risk factor for HCC in our population, this is closely followed by chronic HCV infection. Will probably expect similar trends as in the United States where there has been significant increase in the incidence of HCV related HCC. Based in our experience, abdominal CT scan is the best diagnostic tool to detect these tumors, but we can not recommend its use as the routine screening tool for HCC unless further studies are undertaken. Possibly its use being alternated with abdominal ultrasound would be a more cost effective option.

In our study, the great majority of the patients were

diagnosed with advanced HCC, reason for which only less than half of this group received any kind of therapy. These last two factors are probably responsible for the overall poor survival observed. In view of the generally late diagnosis of hepatocellular carcinoma in our patient population, aggressive education and screening programs should be established and offered to cirrhotic patients if we strive to detect HCC at an early stage.

Resumen

El propósito de este estudio retrospectivo fue estudiar las características del carcinoma hepatocelular en los pacientes veteranos hispanos de Puerto Rico durante un periodo de 10 años (1992 -2002).

Se evaluaron 114 expedientes médicos de pacientes con un diagnóstico confirmado histológicamente de carcinoma hepatocelular.

La edad promedio era de 66.6 años. 82% tenían cirrosis hepática. 60% tenían un historial de enfermedad hepática por alcohol, 38% tenían aerología positiva para hepatitis C. 21% tenían ambos factores de riesgo. Solo 5% tenían hepatitis B crónica. No se encontró ningún otro factor de riesgo. Según la clasificación de Child, el 42% eran clase A, 44% B y 14% C. El CT fue diagnóstico en casi todos los pacientes mientras que el sonograma solo en el 57%. Alfa-fetoproteina fue diagnostica en 32%. La sobrevida promedio fue de 10.3 meses y similar para todos los factores de riesgo. Solo un 42 % de los pacientes recibió algún tratamiento.

La enfermedad hepática por alcohol sigue siendo en nuestra población el factor de riesgo mas importante para el desarrollo de carcinoma hepatocellular, cercanamente seguida por hepatitis C crónica. Solo algunos de nuestros pacientes recibieron tratamiento debido a lo avanzado de la enfermedad al momento de diagnóstico por lo que la sobrevida nuestros pacientes fue en promedio menos de un año. El cáncer hepatocelular continua siendo una enfermedad mortal por esto, la identificación temprana mediante un cernimiento adecuado podría resultar en una mejor sobrevida. Se deben reforzar la educación sobre los beneficios de cernimiento temprano en esta condición.

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