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Hepatocellular Carcinoma in HIV-Infected Patients: Clinical Characteristics and Prognostic Factors

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Abstract

We analyzed 53 HIV-infected patients with hepatocellular carcinoma (HCC) diagnosed at our institution from 1998 to 2012. All patients were coinfected with hepatitis virus (77% HCV; 12% HBV; 11% HCV+HBV), and 95% had liver cirrhosis. HCC was diagnosed under surveillance in 41% of patients. Potentially curative therapy was given to 32% of patients and palliative therapy to 30% patients. Median survival was 2 months in those diagnosed from 1998 to 2005, and 11 months in those diagnosed from 2006 to 2012; P=0.16. Survival was independently associated with HCC stage, alpha-fetoprotein serum levels, MELD score, and any treatment.

Keywords

Hepatocellular carcinoma; Human Immunodeficiency Virus; Hepatitis C Virus; Chronic Hepatitis C; Liver Cirrhosis

Introduction

Each year, more than half a million people worldwide are diagnosed with hepatocellular carcinoma (HCC), and approximately 20,000 of these cases are diagnosed in the United States [1]. Major risk factors for HCC include infection with HBV or HCV, alcoholic liver disease, and nonalcoholic fatty liver disease [1]. It is note worthy that this neoplasm usually appears in patients with underlying cirrhosis.

Since the introduction of combination antiretroviral therapy (cART), the incidence of HCC has increased steadily in HIV-infected individuals, driven primarily by HCV infection [2-4]. Recent reports indicate that HCC is an increasingly frequent cause of death among patients with HIV infection [5].

In comparison with non–HIV-infected patients, some reports suggest that at diagnosis of HCC, patients with HIV infection are younger and more frequently symptomatic with advanced tumors [6,7]. Little is known however about HCC surveillance practices in at-risk HIV-infected patients and about prognostic factors of HCC in this population group. Our objective was to assess clinical characteristics, treatment, and survival in HIV-infected patients with a particular emphasis on identification of prognostic factors.

Methods

We reviewed the Minimum Basic Data Set (MBDS) of our institution to identify all HIV-infected patients diagnosed with HCC at our institution from 1998 to 2012. The MBDS is a computerized database of clinical and administrative data generated from the medical records of discharged patients that is used in hospital management processes and clinical and epidemiological research. Patient medical records were reviewed, and data were extracted according to a protocol and recorded in a working database.

Diagnosis of HCC was based on noninvasive imaging tests or pathology findings according to well-defined criteria [8]. HCC was staged following the Barcelona/Clínic Liver Cancer (BCLC) classification [9]. We compared patients with HCC diagnosed before and after 2005, when the new HCC guidelines of the American Association for the Study of Liver Diseases were published [10]. For the purposes of the study, we

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Table 1: Clinical characteristics, diagnosis, and treatment of HIV-infected patients with hepatocellular carcinoma.

	1998-2005 (n = 19)	2006-2012 (n = 34)	TOTAL (N = 53)	*P*
DEMOGRAPHICS AND HIV				
Male sex	17 (90)	30 (88)	47 (89)	1.00
Age – yr, median (IQR)	44 (41-48)	48 (45-52)	47 (44-50)	<0.01
History of IDU	13 (68)	29 (91)	42 (82)	0.06
CDC category C	5 (26)	15 (48)	20 (40)	0.12
cART	17 (90)	28 (85)	45 (87)	1.00
CD4 + cells/μL, median (IQR)	272 (110-396)	357 (236-614)	326 (185-535)	0.12
HIV-RNA < LLOQ	9 (47)	26 (79)	35 (67)	0.02
Alcohol > 50 g/d	2 (10)	10 (29)	12 (23)	0.17
LIVER DISEASE				
Hepatitis coinfection	19 (100)	34 (100)	53 (100)	1.00
HCV	15	26	41	
HBV	3	3	6	
HCV and HBV	1	5	6	
Liver cirrhosis	19 (100)	32 (94)	51 (95)	1.00
Child-Pugh stage B/C	11 (58)	20 (61)	31 (60)	0.53
Liver decompensation	10 (53)	16 (49)	26 (50)	0.50
MELD score, median (IQR)	12 (9-18)	10 (8-13)	11 (8-15)	0.02
Peg-IFN/RBV therapy	6 (32)	15 (47)	21 (41)	0.22
CHARACTERISTICS OF HCC				
Solitary tumor	6 (32)	14 (41)	20 (38)	0.40
Lesion diameter > 5 cm	12 (67)	15 (44)	27 (52)	0.12
Portal vein invasion	7 (37)	12 (35)	19 (36)	0.57
Metastasis	4 (21)	4 (12)	8 (15)	0.43
BCLC stages C or D	13 (68)	16 (47)	29 (55)	0.11
AFP >200 ng/mL	9 (47)	11 (33)	20 (38)	0.23
DIAGNOSIS OF HCC				
During surveillance	8 (42)	14 (41)	22 (41)	0.60
Biopsy confirmation	7 (37)	5 (15)	13 (24)	0.09
TREATMENT OF HCC				
Treated after diagnosis	8 (42)	24 (71)	32 (60)	0.04
Potentially curative treatment	4 (21)	13 (38)	17 (32)	1.00
RFA/PEI	4 (8)	12 (22)	16 (30)	
Surgical resection	1 (2)	3 (6)	4 (8)	
Liver transplantation	1 (2)	0	1 (2)	
Noncurative treatment	4 (21)	12 (35)	16 (30)	0.42
TACE	6 (11)	9 (17)	15 (28)	
Sorafenib	1 (2)	5 (9)	6 (11)	

Abbreviations: **IDU**, injection drug use; **LLOQ**, lower limit of quantification; **MELD**, Model for End-stage Liver Disease; **HCC**, hepatocellular carcinoma; **BCLC**, Barcelona-Clínic Liver Cancer staging system; **AFP**, alpha fetoprotein; **RFA**, radiofrequency ablation; **PEI**, percutaneous ethanol injection; **TACE**, transarterial chemoembolization

Values are expressed as n (%) unless otherwise specified.

Table 2: Variables associated with survival of HIV-infected patients with hepatocellular carcinoma by Cox regression analysis.

	Univariate Cox regression analysis			Multivariate Cox regression analysis		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
CDC category C	0.76	0.38-1.53	0.44			
cART	0.75	0.27-2.14	0.59			
CD4 cells (%)	0.99	0.95-1.02	0.42			
Detectable HIV-RNA	1.89	0.97-3.67	0.06	0.72	0.34-1.49	0.37
HCV infection	1.16	0.35-3.80	0.81			
Child-Pugh (A vs. BC)	0.87	0.45-1.69	0.68			
Decompensation	0.87	0.45-1.67	0.68			
MELD score	1.09	1.01-1.67	<0.01	1.18	1.08-1.29	<0.001
Alcohol consumption	0.65	0.28-1.48	0.30			
BCLC (CD vs. 0AB)	16.89	6.02-47.43	<0.001	9.97	2.58-38.52	0.001
AFP > 200 ng/ml	3.58	1.83-6.99	<0.001	5.52	2.27-13.45	<0.001
Any treatment	0.13	0.06-0.29	<0.001	0.25	0.08-0.77	0.016
Screening of HCC	0.69	0.35-1.33	0.26			
Diagnosis after 2006	0.64	0.33-1.22	0.17			

Abbreviations: **cART**, combination antiretroviral therapy; **MELD**, Model for End-stage Liver Disease; **BCLC**, Barcelona-Clínic Liver Cancer staging system; **AFP**, alpha-fetoprotein; **HCC,** hepatocellular carcinoma.

considered that the diagnosis of HCC was made during surveillance when ultrasonography of the liver (with no evidence of HCC) was performed within the 12 months before the diagnosis of HCC.

During the study period, a multidisciplinary liver cancer committee met regularly to review cases, outline treatment plans, and follow outcomes of patients with liver cancer. This committee comprises hepatologists, interventional radiologists, and transplant surgeons with expertise in the diagnosis, treatment, and management of liver tumors.

Results

Patient characteristics at the time of diagnosis of HCC are shown in (Table 1). Almost 90% were male, the median age was 47 years, 82% had acquired HIV by injection of drugs, 40% had had prior AIDS defining conditions, 87% were on cART, the median CD4 cell count was 326 cells/μL, 67% had an HIV-RNA load below the limit of quantification, and 23% drank more than 50g of alcohol per day. Of note, in the second period, patients were older and had full suppression of HIV-RNA more frequently than in the first period.

As for liver disease, all patients were coinfected with hepatitis virus (77% HCV; 12% HBV; 11% HCV+HBV), 95% had liver cirrhosis, 60% were Child-Pugh stage B or C, 50% had decompensated liver disease, and 41% had previously received Peg IFN and RBV without achieving a sustained viral response. Patients in the first period had significantly higher Model for End-Stage Liver Disease (MELD) scores than patients in the second period (Table 1).

HCC was diagnosed during surveillance in 41% of patients, with no significant differences between the periods (Table 1).

A nonsignificant trend towards tumors with better prognostic characteristics was found in the second period in comparison with the first period (Table 1). A solitary lesion was found in 38% of patients, and lesions greater than 5 cm in diameter were found in 52% of patients. Portal vein invasion was detected in 36% of patients, and metastases in 15%. The tumor was advanced (BCLC stage C or D) in 55% of patients, and alpha-fetoprotein serum levels were above 200 ng per ml in 38% of patients.

Sixty percent of patients received treatment for HCC. Of note, patients in the second period received treatment for HCC more frequently than patients in the first period. Potentially curative therapy was given to 32% of patients and noncurative therapy to 30% of patients.

The median (IQR) duration of follow-up was 10 (1-23) months. The median (IQR) survival was 2 (1-27) months in the first period and 11 (3-23) months in the second period; *P*=0.16. A nonsignificant trend towards improved survival during the first 3 years after diagnosis of HCC was observed in the second period (1-year survival, 62%; 2-year survival, 37%; and 3-year survival, 28%) in comparison with the first period (1-year survival, 37%; 2-year survival, 26%; and 3-year survival, 14%).

Variables associated with survival by univariate and multivariate Cox regression analysis are shown in (Table 2). Survival was independently associated with BCLC stage, serum alpha-protein levels, MELD score, and any treatment (Figure 1).

Discussion

We analyzed the characteristics, treatment, and outcome of 53 HIV-infected patients with HCC attended in our institution over a 14-year period (1998 to 2012). HCV-related cirrhosis was the most frequent underlying disease, although in a large number of patients, profound immunosuppression and alcohol consumption - well known enhancers of fibrosis progression in HIV/HCV-coinfected individuals [3,11,12] - were associated with advanced liver disease.

Of note, only 40% of tumors were detected in surveillance programs, irrespective of the period analyzed; this figure differs little from data reported elsewhere [13]. It must be remembered that ours is a referral center for liver-transplantation and that a substantial proportion of patients were already diagnosed with HCC when first seen by us. We found that HCC was more frequently diagnosed

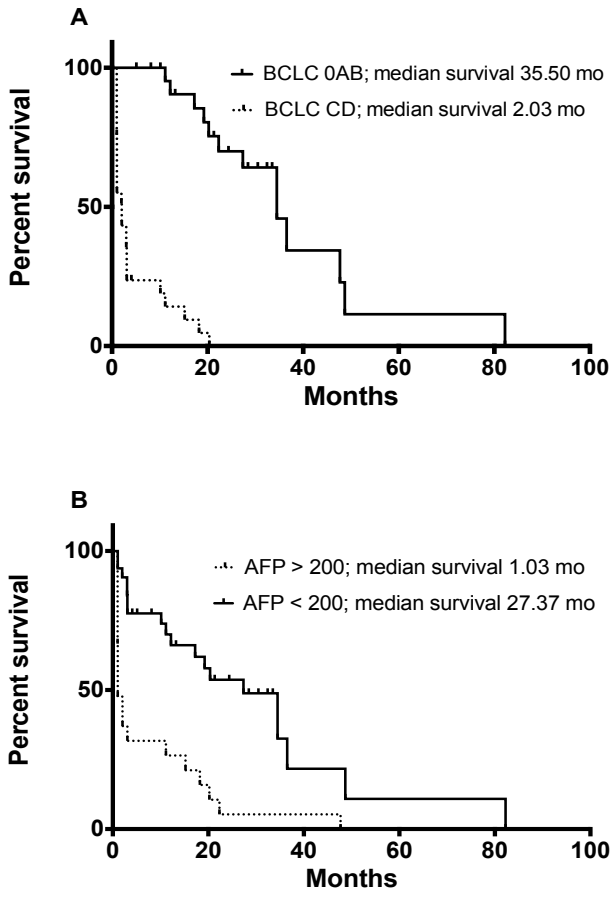

Figure 1: Kaplan-Meier estimates of survival according to the Barcelona/ Clínic Liver Cancer (BCLC) classification. The median survival was 35.50 months for nonadvanced stages (BCLC 0AB) and 2.03 months for advanced stages (BCLC CD) (Figure 1A). Kaplan-Meier estimates of survival according to serum alpha-fetoprotein (AFP) levels. The median survival was 1.03 months for patients with AFP >200ng/ml and 27.37 months for patients with AFP <200ng/ml (Figure 1B).

using noninvasive imaging tests after 2005, thus reflecting current recommendations [1]. At diagnosis, HCC was frequently advanced, and half of the patients had decompensated liver disease; these findings are concordant with those of other studies in this field [6,7].

A significantly higher proportion of patients received treatment for HCC after 2005. The explanation for this finding is multifactorial: in recent years, a more generalized approach to managing malignant diseases in HIV-infected patients has been applied following the appropriate-for-stage recommendations used in the general population; in addition, new treatments for HCC, such as sorafenib, have become available.

Anonsignificant trend towards increased survival was observed after 2005. However given that the statistical power of the comparisons of mortality between the 2 periods ranged from 20% for 3-year survival and 40% for 1-year survival, a type II error could not be excluded. We found that survival was independently associated with tumor burden (BCLC stage and serum alpha-fetoprotein concentration), liver function (MELD score), and treatment of HCC. Detectable HIV-RNA was associated with an increased hazard of mortality by univariate analysis but not by multivariate analysis.

Our study is limited by its retrospective design, and by the small number of patients included. In addition, although the AASLD screening guidelines were enforced in our institution after their publication in 2005; we have no data about how diligently they were followed by clinicians. We recognize that the definition of diagnosis of HCC during surveillance used in this study (ultrasonography within the 12 months before the diagnosis of HCC) doesn't match with current recommendations that surveillance be undertaken at 6 monthly intervals [14]. However, it must be taken into consideration that the ideal surveillance interval is not known; and that a surveillance interval of 6-12 months has been proposed based on tumor doubling times [14]. Moreover, a retrospective study has reported that survival is no different in patients screened at 6 or 12 monthly intervals [15]. Nevertheless our results reflect the experience of a single institution in which a multidisciplinary team reviewed HCC cases and outlined treatment plans. Our findings allow us to draw some conclusions that we believe are relevant for clinical practice. First HCV-related cirrhosis was by far the most frequent underlying disease in patients with HCC many of whom had a history of severe immunosuppression and/or alcohol consumption. Consequently, key preventive measures for HCC among HIV/HCV-coinfected individuals should include interventions that modify the natural history of HCV infection such as antiviral therapy for HCV [16] and HIV [17] and avoidance of alcohol and injection drugs. Second most cases of HCC were detected outside surveillance programs. Third at the time of diagnosis, half of the patients already had decompensated liver disease and the tumor was frequently advanced. These findings highlight the need to prioritize identification of patients at risk of HCC particularly those with liver cirrhosis. Patients can be identified accurately using noninvasive methods such as transient elastography and serum tests [18]. Following current guidelines patients at risk should be screened for HCC with 6-monthly liver ultrasound with or without serum alpha-fetoprotein testing [10], a procedure that is associated with significant improvements in early tumor detection, administration of curative therapy and overall survival in patients with cirrhosis [19].

Shortening the interval for HCC screening has been proposed for HIV-infected patients with liver cirrhosis since development of HCC could be more rapid in this group than in cirrhotic patients without HIV-infection [20]. This approach warrants further analysis in prospective studies, particularly in patients at high risk of developing liver-related events such as those with liver-stiffness values ≥40kPa [21,22].

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