Tratamiento e historia natural de la hepatitis crónica C en pacientes coinfectados por VIH-1

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Tesis Doctoral

TRATAMIENTO E HISTORIA NATURAL DE LA HEPATITIS CRÓNICA C EN PACIENTES COINFECTADOS POR VIH-1

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Original article

Increased incidence of hepatocellular carcinoma (HCC) in HIV-1 infected patients

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Abstract

Background: The likely increased incidence of hepatocarcinoma (HCC) in HIV-1 infected patients has not yet been demonstrated.
Methods: We studied all cases of HCC occurring in HIV-1 infected patients in our hospital during the past 15 years. Incidence and survival time were compared with those of the general population in the same area and the same time of the study.
Results: We found 6 cases of HCC in a cohort of 2383 HIV-1 infected patients between 1986 and 2001. This is a higher than expected incidence rate of HCC compared with the general population, with a standardized incidence ratio of 13.95. Chronic hepatitis virus infection and alcohol abuse were present in four and two cases, respectively. In one patient, no liver disease was known before the HCC and the surrounding liver was normal in the necropsy study.
Conclusion: The improved survival of patients on highly active antiretroviral treatment (HAART) and the increasing incidence of end-stage liver disease in these patients caused by chronic hepatitis virus infection and alcohol abuse may be responsible for an increase in the incidence of HCC in HIV-1 infected patients.

Keywords: Chronic hepatitis; Hepatocellular carcinoma; HIV infection; Liver cirrhosis

1. Introduction

As a result of highly active antiretroviral therapy (HAART) and close clinical control of opportunistic infections [1], the pattern of mortality and morbidity in HIV-1 infected patients has changed dramatically [2,3]. End-stage liver disease (ESDL) has become an important cause of death and hospital admissions [4,5], explained not only by the high incidence of hepatitis C virus (HCV) infection, but also by an accelerated course of chronic hepatitis C in co-infected patients [6,7]. Liver cirrhosis constitutes the main risk factor for HCC, with the highest risk associated with cirrhosis due to chronic infection by hepatitis B and hepatitis C virus. Therefore, in these patients, hepatocellular carcinoma (HCC) is expected to appear with increasing incidence and earlier in the course of the HCV infection. However, the association of liver cancer with HIV infection/AIDS has not been previously confirmed in cohort studies, and few reports have mentioned HCC cases in HIV-1 infected patients [8,9].

Recently, in a study comparing the incidence of HCC before and after HAART, an increase in HCC cases was reported [10]. This is probably due to the long time needed for the development of HCC.

2. Patients and methods

We describe the cases of HCC occurring in HIV-1 infected patients followed up in our hospital over the past 15 years. This hospital is located in the Balearic Islands in

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southern Europe and provides care to a population with a high rate of intravenous drug use and a high incidence of AIDS (87.92 per million in 2001; European incidence 23.3 per million). Incidence and survival time were compared with those of the general population in the same area and the same time of the study.

A chart review of cases of HCC was conducted in a cohort of 2383 HIV-1 infected patients between 1986 and 2001. At the time of analysis, 589 had died and 1454 were still being followed up. Person-years at risk were 35,745. Cancer incidence rates were calculated using the person-years method. Standardized incidence ratios were obtained by dividing the observed number of cases by the expected number. The expected number was calculated based on incidence rates registered between 1986 and 2001 in the general population-based cancer registries of Mallorca.

3. Results

Of the 2383 patients followed up, 72.9% were males with a mean age of 38.4 years; 48.15% of them were diagnosed as having AIDS. Some 54.8% of the 2383 were co-infected with HCV (EIA-positive for HCV antibodies) and 11.9% were co-infected with hepatitis B virus (HBV), considering only those with positive surface antigen. No cases of HCC were described until 1996. Since 1996, six patients with HCC have been diagnosed. The incidence of liver cancer in HIV-infected patients between 1986 and 2001 was 63 cases/100.000 persons per year. The incidence of HCC in the general population in Mallorca was 4.49 cases/100,000 persons per year. Observed cases were 6 and expected cases were 0.43; the standardized incidence ratio (SIR) was 13.95.

The main clinical features of the six patients with HCC are summarized in Table 1. All of the patients were male and older than the mean age (38–61 years, median age 49.66 years). The duration of the HCV infection was unknown in all of them. Two of the six were AIDS patients. Their CD4 cell count was between 70 and 359 cells/il (median 198 cells/μl). The HIV viral load was under the detection limit (200 copies/ml by PCR) in three of them. Only two were on HIV treatment with three drugs; in one patient, HIV RNA was undetectable on two nucleoside analogues, and two of the six died before new drugs became available. Another patient refused to take more pills.

Liver disease etiology was HCV infection and alcohol abuse in three patients; HCV, HBV, HDV, and alcohol in one patient; and alcohol abuse with negative viral markers in another. The sixth patient did not have known liver disease. He was a teetotaler, with no known exposure to potential liver carcinogenics, with negative viral markers. Infiltrative, metabolic, and autoimmune diseases were not found. A necropsy study showed a normal liver with negative immunofluorescence for hepatitis B. In this patient, HIV infection was considered the only risk factor for the development of HCC.

Prior to the development of HCC, some decompensation for end-stage liver disease (ESLD) had occurred in two patients.

Four cases were diagnosed following their referral due to abdominal pain, and two were detected during ultrasound examination performed as a routine test in cirrhotic patients. Alpha-fetoprotein (normal value 0–8 ng/ml) ranged from 76 to 900 ng/ml (median 530 ng/ml). Cytological confirmation was obtained in three cases by fine needle aspiration (FNA); the other three were diagnosed by a suggestive radiological image along with elevated alpha-fetoprotein.

Two patients underwent chemoembolization. One of them was re-treated with radiofrequency ablation and the other only underwent radiofrequency ablation.

For the general population, the median survival time was 6 months; 1-year survival was 22% and 5-year survival was 1%. For HIV-1 infected patients, the median survival time was 3 months (range 1–14 months); only one survived the first year.

Table 1
Main clinical features of the patients with HCC

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	Male	Male	Male	Male	Male	Male
Age	38	42	57	53	62	47
CDC	A2	A3	A3	A2	C3	C3
CD4 (cells/μl)	324	242	145	359	70	154
HIV viral load (PCR; copies/ml)	<200	NA[a]	230.508	NA[a]	<200	<200
Antiretroviral treatment	AZT/DDI	AZT/DDI	D4T/3TC	AZT/DDC	D4T/3TC/NFV[b]	AZT/3TC/NVF/EFV[c]
HCV EIA	NEG	POS	POS	NEG	POS	POS
HBV surface antigen	POS	POS	NEG	NEG	NEG	NEG
Alcohol>80 g/day	Non	Yes	Yes	Non	Yes	yes
CPC[d]	A	A	B	A	B	B
Previous ESLD	None	None	Variceal bleeding, ascites, spontaneous bacterial peritonitis	None	Ascites	None
Year of HCC diagnosis	1999	1997	1999	1996	2000	2001

[a] Not available.
[b] Nelfinavir.
[c] Efavirenz.
[d] Child Pugh class.

4. Discussion

Large population-based studies have shown that HIV-1 infected patients are at an increased risk of cancer other than non-Hodgkin's lymphoma and Kaposi's sarcoma. The most common non-AIDS-related cancers are Hodgkin's disease, lung cancer, lip cancer, testicular seminoma, and even multiple myeloma. It is difficult to determine to what extent the excess of these cancers is associated with HIV/AIDS-related immunosuppression. Interpretation is complicated by shared risk factors such as an increased risk of papillomavirus infection and cigarette smoking [11,12]. Some cancers, especially lung cancer, have a poor prognosis in HIV-1 infected patients. In these cohort studies, mainly performed during the pre-HAART era, no increase in the incidence of liver cancer was reported.

In our patients, we found an increased incidence of HCC. Although this seemed plausible because of the increased incidence of HCV and HBV infection and alcohol abuse in HIV-1 infected patients, it had not been previously confirmed in cohort studies. As previously described for lung cancer, HCC in HIV-1 infected patients could very well have a poor prognosis, as observed in our cases.

Aggressive management of hepatitis virus co-infection (treatment of HCV and HBV and HBV vaccination), alcoholism withdrawal, and early detection of HCC in HIV-1 infected cirrhotics should be encouraged. Further studies are needed to clarify whether HIV infection may have an etiological role in HCC, as suggested in in vitro studies [13], or whether the development of HCC may be favored or accelerated by the immunosuppression associated with HIV/AIDS.

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