

A PEER-REVIEWED ARTICLE

Hepatocellular carcinoma and HIV: Is there an association?

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HIV care providers have seen remarkable progress in treatment options for HIV in the past two decades; subsequently many issues that were not of primary concern in the HIV-infected patient, such as hypertension or hepatitis co-infection, have now become concerns that the HIVcare clinician must address. During the first ten to fifteen years of the epidemic, hepatocellular carcinoma (HCC) was rarely seen in HIV-infected persons; instead opportunistic infections caused such high mortality that patients often did not live long enough to develop HCC. Because the use of highly active antiretroviral therapy (HAART) has prolonged the lives of many HIV-infected individuals and led to a decrease in both morbidity and mortality, HCC has risen as the leading non-AIDS cause of death in co-infected persons.

In the United States, approximately 30% of patients with HIV are co-infected with chronic hepatitis C (HCV), 10% with chronic hepatitis B (HBV), and 1% with both chronic hepatitis B and C. If intravenous drug use is the risk factor for a patient for his/her HIV infection, studies have shown up to a 90% chance that the patient will be positive for hepatitis C antibody. Many studies have also shown that HIV co-infection has a marked effect on acceleration of the progression of both chronic hepatitis B and C.

For patients who are infected with chronic HCV, approximately 5-20% either have or will develop cirrhosis over time. Of those that develop cirrhosis, approximately 1-5% will develop HCC. For the co-infected patient, there is a two-fold increase in the risk of development of cirrhosis and a six-fold increase in the risk of end-stage liver disease as compared to the mono-infected HCV+ patient in a study by Graham *et al*. In a meta-analysis including data from 16,750 patients with HCV, of whom 6242 also had HIV, Ding *et al* showed that there was an overall odds ratio for histological cirrhosis, decompensated liver disease, liver cancer, or death of 3.40 (95% CI = 2.45 and 4.73).

HCC is the commonest primary cancer of the liver and has become the fifth commonest malignancy worldwide. The highest incidence is in Asia (over 20 cases/100,000 people) and sub-Saharan Africa, followed by Italy, Spain, and Latin America, with some of the lowest incidence reported in the United States, Canada, and Scandinavia (less than 5 cases/100,000). Although there is a relatively low incidence in the US, the annual incidence has risen by 80% over the past decades, with the largest increase in the African-American male population as compared to Caucasian men. In western countries, over 90% of cases of HCC occur in those with cirrhosis, while in Asia and Africa the majority of cases of HCC occur in those *without* cirrhosis.

Several risk factors for HCC have been elucidated. The major risk factor is cirrhosis of the liver, although up to 25% of HCC cases in the US do not have any known risk factors. If a patient develops cirrhosis secondary to HCV infection, there is an *annual* risk of 1-4% for development of HCC.

The annual risk for development of HCC for asymptomatic hepatitis B surface antigen (HBsAg) carriers is 0.5% and for patients with chronic hepatitis B is 0.8%. In one study involving 350 patients from Western Europe with compensated cirrhosis from HBV who were followed for six years, the five-year cumulative incidence of development of HCC was 6%. Another retrospective study from Europe revealed a 9% five-year incidence irrespective of hepatitis B e antigen (HBeAg) or HBV DNA (HBV viral load) status at time of diagnosis of cirrhosis; a study by Tsai *et al* in Taiwan showed the association with HBV DNA levels and HCC was in older patients, rather than those less than 40 years of age. HBV leads to chronic inflammation with fibrosis and hepatocyte proliferation and may encode oncogenic viral proteins. HBV genotype influences the development of HCC also; in Asia genotype C has a higher association than genotype B and in North America and Europe genotype D more than genotype A. For those without cirrhosis, the risk factors shown by Liu *et al* to increase the chance of HCC in those with chronic HBV included male gender, BCP T1762/A1764 mutation, and viral load >10⁵ copies/ml.

Patients who are infected with both chronic HBV and HCV have an even higher risk of development of HCC than either disease alone. Comparing the risk of development of HCC after 10 years for HCV mono-infection, HBV mono-infection, and HCV/HBV co-infection revealed an incidence of 16%, 28%, and 45% respectively. A meta-analysis of 32 studies revealed an OR for development of HCC of 20.4 for HBsAg+/HCV neg patients, 23.6 for HBsAg-/HCV+ patients, and 135 for HBsAg+/HCV+ patients, indicating more than simply an additive effect of the two viruses. HBsAg+ patients who are co-infected with hepatitis D develop cirrhosis and HCC at an

average of 48 years versus 62 years for those who only have HBsAg.

So what effect does HIV have on the incidence of HCC development? Clifford *et al* in 2008 performed a case-control study of HCC nested within the Swiss HIV Cohort Study to determine the effect of immune suppression and HAART use on the development of HCC for PLWHA (people living with HIV or AIDS). A total of 85,821 person years were followed with 25,976 of these in women. Thirty-nine patients with primary liver cancers were identified; 12 had liver lymphoma and one had small cell carcinoma so they were excluded. 10 controls were chosen for each case. HBsAg, HCV Ab, or both data were missing from 15.4% of the HCC cases and 13.5% of the control. Men made up 92.3% of the cases with 61.5% of cases in males between 30 and 39 years of age. Ten of the HCC HIV+ patients had HBV co-infection, 11 had HCV co-infections, and five had both co-infections. CD4+ cell count at enrollment, nadir CD4 counts, HIV viral load, and HAART use were *not* associated with HCC but associations were found for latest CD4+ cell count (OR per 100 cells/mcl decrease of 1.33) and a history of an AIDS diagnosis (OR 2.40, 95% CI 1.06-5.44). These associations were stronger for MSM patients than for those with a history of IVDU.

Salmon-Ceron *et al* in France in 2009 analyzed the effect of HIV co-infection on the development of HCC using the French national Mortalite 2005 study as compared to the Mortalite 2000 study. There were 1042 deaths recorded in 2005 as compared to 964 in 2000. In 2005, 44% of those who died were co-infected with at least one hepatitis virus, primarily HCV. Liver-related deaths were reported in 138 patients; heavy alcohol use was significantly more common in these patients than in those who died from other causes, especially for those with HCV or HCV/HBV co-infection as compared to those with HBV co-infection. The underlying cause of liver-related death was decompensated cirrhosis in 66%, hepatocellular carcinoma in 25%, other complications of HCV in 2%, HBV reactivation in 0.7%, and other causes in 6%. Of those with HCC, 80% were male, 60% were tobacco smokers, 41% excessive alcohol consumers, and 9% diabetics. HCC increased among liver-related deaths from 16/110 (15%) in 2000 to 35/138 (25%) in 2005 (p=0.04). This was despite improved control of HIV infection (CD4+ cell counts 157 in 2000 versus 231 in 2005).

An editorial in 2009 by Mark Sulkowski, one of the leaders in hepatitis co-infection research, reviewed the results of many other studies which have been evaluated. Two studies he cited from the United States included a study from Giordano *et al* (1992-2001) that showed a five-fold increase in risk of HCC as compared to those with HCV alone and a prospective observational cohort study by Patel *et al* (1992-2003) that observed a 7.7-fold increased incidence of liver cancer in HIV+ persons as compared to the general population. Dr. Sulkowski recommends that "clinicians caring for HIV/HCV infected patients with advanced fibrosis (bridging fibrosis or cirrhosis) must incorporate HCC screening as part of their routine medical practice." This screening should include serial radiologic imaging of the liver and possibly in conjunction with measurements on a routine basis of alpha-fetoprotein; monitoring of alpha-fetoprotein alone is insufficient to detect all HCC development.

Other factors have been associated with increasing or decreasing the chance of development of HCC and patients should be counseled. These may include schistosomiasis infection, aflatoxin B1 heavy exposure, pesticide exposure, and the presence of diabetes mellitus. Dietary interventions thought to possibly decrease the risk of development of HCC include miso soup and other soya foods, coffee drinking, and diets high in milk, wheat, vegetable, fish, and fruit contents, although studies regarding these foods are conflicting in data.

Although the amount of increased risk of development of hepatocellular carcinoma in HIV+ persons co-infected with hepatitis B or C has yet to be clearly determined, the commonality of co-infection makes this a concern for HIV care clinicians. Hepatitis C co-infection primarily increases the risk of HCC in the presence of cirrhosis, especially if alcohol use is heavy, so screening for those with cirrhosis regularly is important. Hepatitis B co-infection increases the risk at all stages of the disease so screening should be performed for all patients in this setting. Active promotion of both tobacco and alcohol cessation should be emphasized for patients co-infected with either hepatitis virus. ♦

EDITOR'S NOTE: Alcohol screening tools are available at projectcork.org/clinical_tools/

REFERENCES

- Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22,707 men in Taiwan. *Lancet* 1981; 2: 1129-33
- Chiaromonte M, Stroffolini T, Vian A *et al*. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999; 85: 2132-7
- Clifford GM, Rickenbach M, Polesel J *et al*. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. *AIDS* 2008; 22(16): 2135-41
- Deng LP, Gui XE, Zhang YX, Gao SC, Yang RR. Impact of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *World J Gastroent* 2009 Feb 28; 15(8): 996-1003

Giordano TP, Kramer JR, Soucek J, Richardson P, El Serag HB. Cirrhosis and hepatocellular carcinoma in HIV-infected veterans with and without the hepatitis C virus: a cohort study, 1992-2001. *Arch Intern Med* 2004; 164: 2349-54

Gomaa AI, Khan SA, Toledano MB, Waked I, Taylor-Robinson SD. Hepatocellular carcinoma: Epidemiology, risk factors and pathogenesis. *World J Gastroent* 2008 July 21; 14(27): 4300-8

Graham CS, Baden LR, Yu E *et al*. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001; 33: 562-69

Kao JH, Chen PJ, Lai MY, Chen DS. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. *Gastroenterology* 2003; 124: 327-34

Liu CJ, Kao JH. Hepatitis B virus-related hepatocellular carcinoma: epidemiology and pathogenic role of viral factors. *J Chin Med Assoc* 2007; 70: 141-5

Michielsen PP, Francque SM, van Dongen JL. Viral hepatitis and hepatocellular carcinoma. *World J Surg Oncol* 2005; 3: 27

Ni YH, Chang MH, Wang KJ *et al*. Clinical relevance of hepatitis B virus genotype in children with chronic infection and hepatocellular carcinoma. *Gastroenterology* 2004; 127: 1733-8

Patel P, Hanson DL, Sullivan PS *et al*. Incidence of types of cancer among HIV-infected persons compared to the general population in the United States, 1992-2003. *Ann Intern Med* 2008; 148: 728-36

Realdi F, Fattovich G, Hadziyannis S *et al*. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP). *J Hepatol* 1994; 21: 656-66

Salmon-Ceron D, Rosenthal E, Lewden C *et al*. Emerging role of hepatocellular carcinoma among liver-related causes of death in HIV-infected patients: the French national Mortalite 2005 study. *J Hepat* 2009; 50: 736-45

Sulkowski M. Hepatocellular carcinoma in HIV-infected patients comes of age: The convergence of epidemiology and treatment effectiveness. *J Hepat* 2009; 50: 655-8

Tsai FC, Liu CJ, Chen CL *et al*. Lower serum viral loads in young patients with hepatitis B-virus-related hepatocellular carcinoma. *J Viral Hepat* 2007; 14: 153-60

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