Cancer Chemother Pharmacol (1994) 33 (Suppl): S 153–S 154

Cancer Chemotherapy and Pharmacology

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Occurrence of hepatocellular carcinoma in chronic viral hepatitis

Masao Omata[1], **Susumu Takano**[2]

[1] Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo, Japan
[2] Division of Gastroenterology and Hepatology, Kawasaki Chuo Hospital, Kawasaki, Japan

In the general population of Japan, the carrier rates of hepatitis B virus (HBV) and hepatitis C virus (HCV) are in the same range (1.3% and 1.5%, respectively) [16]. However, HBV and HCV carriers account for 20% and 70% of hepatocellular carcinoma (HCC), respectively (original data, not shown). According to the data reported by the Ministry of Health and Welfare of Japan, 17,000 HCV antibody-positive and 7,000 HBV surface antigen (HBsAg)-positive HCC patients die each year. Therefore, the relative risk of developing HCC in HCV carriers should be larger than that in HBV carriers. On the other hand, the relative risks of developing HCC in cirrhotic patients is about the same, regardless of the etiology [3, 17]. However, the relative risk of developing HCC in patients with chronic hepatitis of various etiologies has not yet been evaluated.

The occurrence of HCC was investigated in 251 patients with hepatitis B (127 patients) and hepatitis C (124 patients) with an average follow-up period of about 70 months. All patients were diagnosed by liver biopsy, and the histological diagnoses were chronic persistent hepatitis and chronic active hepatitis. Patients were followed at outpatient clinics on the basis of the ultrasonographic findings and the serum alpha-fetoprotein (AFP) level. When mass lesions were detected or the serum AFP level increased, additional diagnostic procedures were added, including enhanced computed tomography, angiography, and ultrasound-guided biopsy of neoplastic lesions.

As a result, HCC was detected in 10.4% of the 124 C-viral chronic hepatitis patients and 3.9% of the 127 B-viral chronic hepatitis patients. Thus, the relative risk of developing HCC was 2.7 times higher in chronic hepatitis C patients than in chronic hepatitis B patients. According to liver biopsy specimens of nonneoplastic lesions taken on the same day of ultrasound-guided liver biopsy of neoplastic lesions, noncirrhotic liver was seen in 7.7% of the C-viral HCC cases versus 40% of the B-viral HCC cases. The period between the initial liver biopsy and the diagnosis of HCC was shorter in the former cases as the liver disease was more advanced in chronic hepatitis C. However, no obvious relationship between the initial liver biopsy and the duration was detected with hepatitis B.

In chronic hepatitis C, HCC developed exclusively in the cirrhotic liver cases, whereas it developed in cases of less advanced chronic liver disease in the chronic hepatitis B patients. This phenomenon might be due to a different form of progression of the B-viral and C-viral chronic liver diseases. In chronic hepatitis C, the progression of disease was not rapid in any of the cases, without exception. Resolution was seen in a few cases, and a majority of the patients progressed to advanced liver disease over a period of several decades [2, 7, 10]. The clinical course of chronic hepatitis C is monotonous, and sequellae of this disease are easy to predict. However, clinical resolution was often seen in chronic hepatitis B after inactivation of viral replication as shown by negativity of the serum for HBV-DNA or HB e seroconversion [8, 14, 19]. On the other hand, HCC developed in the nonneoplastic liver in cases of chronic hepatitis B. Therefore, the clinical course of chronic hepatitis B shows wide variety. Some cases progress rapidly to HCC, whereas clinical resolution is seen in other cases.

The differences in the histopathology of the nonneoplastic lesions in B-viral HCC and C-viral HCC might arise from the role of virus infection in hepatocarcinogenesis. To our knowledge, integration of the viral gene into the host chromosome has not been reported in chronic HCV infection. Integration of the HBV gene into the host chromosome is seen not only in HCC but also in cirrhosis and less advanced chronic liver disease [1]. Although hepatocarcinogenesis of HBV has not been established by direct evidence, the integrated HBV genome might play some role in hepatocarcinogenesis. Alteration of the host chromosomal DNA [11], an excess of preS/S protein in the cytoplasm of hepatocytes [4], and transcriptional trans-activating activities of the X gene [18] are the major hypotheses regarding hepatocarcinogenesis of the HBV gene.

Work presented at the Third International Symposium on Treatment of Liver Cancer, Seoul, Korea, 12–13 February 1993

Correspondence to: Susumu Takano, Division of Gastroenterology and Hepatology, Kawasaki Chuo Hospital, Tamachi 2-9-1, Kawasaki 210, Japan

Thus, hepatocarcinogenesis in chronic hepatitis C might be directly related to the cirrhotic state itself.

In chronic hepatitis C, the most efficient therapeutic approach for interrupting the development of HCC is thought to be the induction of resolution before the disease has advanced to cirrhosis of the liver. Many investigations have been reported about interferon treatment for chronic hepatitis C. Resolution defined as normalization of the serum ALT level could be obtained in some cases, but it has not been clearly established whether interferon treatment can terminate HCV infection or induce its histological resolution before it advances to cirrhosis [5, 6, 9, 11, 12]. We have previously reported the results of a preliminary trial in which acute hepatitis C could be resolved before it advanced to a chronic condition by treatment with natural beta-interferon [13]. Resolution of acute non-A, non-B hepatitis was achieved in 10 of 11 cases treated by beta-interferon administration, whereas 11 of 14 control cases advanced to chronic hepatitis [13]. This approach is thus thought to be the most efficient method for decreasing the occurrence of HCC in chronic hepatitis C.

In conclusion, the occurrence of HCC was about 3 times more frequent in chronic hepatitis C than in chronic hepatitis B, but HCC developed in the noncirrhotic liver only in cases of chronic hepatitis B. The development of HCV-derived HCC can be prevented by interferon treatment in cases of acute and chronic hepatitis infections.

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