Viral hepatitis, by either hepatitis C virus (HCV) or hepatitis B virus (HBV), is the dominant cause of hepatocellular carcinoma (HCC). This is to say that HCC may be prevented by controlling viral infection. Horizontal transmission of HCV has become obsolete owing to the discovery of the virus. Vertical transmission of HBV during delivery has been effectively prevented by vaccination and immunization of neonates. The efficacy of interferon therapy against HCV was recently much improved. We now possess several powerful antiviral drugs against HBV. There has been progress also in the treatment of HCC, and together with advances in diagnostics facilitating HCC detection at an early stage, tumor nodules can often be completely removed either by medical ablation or surgical resection. Nevertheless, recurrence of HCC after apparently curative treatment is extraordinarily frequent, since the remaining liver is still at a particularly high risk of HCC. An effective treatment of HCC should include measures to control de novo carcinogenesis. (Liver Transpl 2004;10:S111–S114.)

Hepatocellular carcinoma (HCC) is unique among cancers in that the acquired factors are directly responsible for carcinogenesis in the majority of cases. In particular, HCV infection forms the predominant basis of HCC development in various countries, whereas HBV is the main etiology in regions where its infection is prevalent. In Japan, HCV is causative in 80% and HBV in 10% cases of HCC. This implies two important things. First, it is possible to distinguish the patients at high risk for HCC, facilitating efficient screening for HCC development. Second, HCC can be prevented, at least theoretically, by controlling the acquired factor, viral infection.

Prevention of Viral Infection

Strategies for HCC prevention can be made at two levels: the prevention of virus infection and the treatment of viral hepatitis. In Japan and other countries, neonates from HBV-positive mothers are treated with the combination of hepatitis B vaccination and hepatitis B immune globulin (HBIG). This procedure has been practiced in Japan since the 1980s. It effectively prevents the infection during delivery, the main route of HBV transmission, although intrauterine infection remains a possibility. Thus, the rate of mother–neonate vertical transmission of HBV has been reduced down to one-twentieth of the previous rate. The prevalence of an HBV carrier in Japan is significantly lower among the younger generation than among the older ones. HBV prevention is said to be one of the most conspicuous achievements of public health policy.

In Japan, HCV transmission also seems to have been decreasing for a couple of decades, possibly owing to the improved hygienics in general medical practice. However, we were not able to effectively prevent the blood transfusion-mediated HCV infection, or non-A, non-B hepatitis, as it was called then, until the discovery of HCV in the late 1980s. With subsequent improvements in HCV detection, the occurrence of HCV infection has become virtually obsolete, although transmission through intravenous drug abuse remains a threat.

Taken together, transmission of HBV and of HCV has been effectively controlled for years in Japan, and the incidence of HCC will doubtless be decreased in the future. Nevertheless, the incidence of HCC has been rising since the 1970s and has not yet started to decline. This is because the risk of HCC in infected patients is actually increasing as the patients grow older. Consequently, treatment for viral hepatitis remains a matter of great clinical importance.

Treatment of Chronic Hepatitis C

HCC in Japan is characterized by the 8:1 predominance of type C over type B, while the prevalence of HBV and HCV infection in the Japanese general population is estimated at about 1.5% each. Consequently, the odds ratio for HCC as against the uninfected population is 500 with HCV infection and 65 with HBV infection. The risk ratio for lung cancer posed by smoking is about 10. Helicobacter pylori infection may be associated with stomach cancer with a similar risk ratio. Thus, patients with HCV infection can be considered to constitute a super-high-risk group. The risk of HCC does differ among patients with HCV infection: it is

Abreviations: HCC, hepatocellular carcinoma; HBIG, hepatitis B immune globulin; ALT, alanine aminotransferase; PEG, polyethylene glycolated; HBV, hepatitis B virus; HCV, hepatitis C virus.

From the Department of Gastroenterology, University of Tokyo, Japan.

Address reprint requests to Masao Omata, M.D., Professor & Chair, Department of Gastroenterology, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Telephone: 81-3-5800-6524; FAX: 81-3-5800-6528; E-mail: omata-2im@h.u-tokyo.ac.jp

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negligible in asymptomatic healthy carriers and as high as 6% per year in cirrhotic patients.4–6 The latter value is more than 2,000 times the incidence of HCC in the population without hepatitis virus infection. Thus, hepatitis virus infection, especially infection by HCV, is by far the strongest acquired risk factor known for any carcinogenesis.

Shortly after the discovery of HCV, the effectiveness of interferon therapy against hepatitis C virus infection was confirmed.7,8 Interferon monotherapy was licensed by the Japanese national health insurance program in 1992, and more than 200,000 patients with chronic hepatitis C were treated. By the licensed 6-month protocol of interferon monotherapy, about 30% of the treated patients showed sustained virologic response. Pretreatment factors predictive for the response were extensively studied, showing that serum low virus load and non-1b HCV genotypes are the strongest factors facilitating the virologic response.

In 1994, we set up a national surveillance program for HCC development among chronic hepatitis C patients and enrolled about 2,900 biopsy-proven cases; 2,400 of them received interferon treatment, showing a sustained virologic response rate of 33% on average.6,9,10 The reduction in the risk of HCC by interferon therapy was confirmed by multivariate Cox proportional hazard regression controlling for age, gender, and the stage of liver fibrosis.6 Compared to untreated patients, the risk of HCC was reduced by half among the interferon-treated patients as a whole, and down to one-fifth among sustained virologic responders. We also confirmed histologically the resolution of cirrhosis following sustained virologic response.9 About 10% of the patients showed sustained normalization of serum alanine aminotransferase (ALT) levels after interferon therapy in spite of continued HCV viremia. HCC incidence was reduced also among these patients as compared to the untreated ones. However, longer-term observation revealed that active hepatitis may recur despite in the biochemical responders with viremia.

About 70% of HCV found in Japan belongs to the 1b genotype. Infection with this genotype is usually accompanied by high serum virus load and resistance to interferon therapy. Sustained virologic response rate in 1b genotype high-virus-load infection is less than 10% with the licensed 6-month interferon monotherapy, in marked contrast to the rate of 60% in non-1b genotype infection.11 Combination with ribavirin is known to improve the efficacy of interferon.12 In Japan, the duration of the combination therapy is currently limited to 6 months, resulting in a response rate of only about 15% in 1b genotype high-virus-load infection. In the near future, however, polyethylene glycolated (PEG) interferon will be introduced in Japan. PEG interferon can be given on a once-a-week basis and improvement is anticipated in compliance.13 A sustained virologic response rate of over 40% is expected with the combination of PEG interferon and ribavirin for 48 weeks in 1b genotype high-virus-load infection.14

Activity of hepatic inflammation and the progression rate of fibrosis varies widely among individual patients with HCV infection. Some patients never have active hepatitis in their lifetime. An asymptomatic healthy carrier at 70 years of age has virtually no possibility of ever developing HCC or liver failure. On the other hand, patients at 40 years with moderate liver fibrosis stand a substantial risk of HCC development sometime in their lifetimes. The indication of interferon therapy must be considered on the basis of expected lifetime risk of HCC development, which is dependent on the present fibrosis stage and life expectancy, together with the possibility of achieving sustained virologic response deduced from viral genotype and load. If liver biopsy is not feasible, the stage of liver fibrosis can be estimated from laboratory data, the platelet count, or prothrombin activity, in particular.

### Treatment of Chronic Hepatitis B

Although HBV infection is a definite risk factor for HCC development, the risk ratio can be crudely estimated at one-eighth that of HCV infection. The stage of liver fibrosis and the risk of HCC are not as strongly associated in chronic hepatitis B as in hepatitis C.15 Thus, it is less easy to distinguish a high-risk group of HCC among chronic hepatitis B patients. Interferon had been used to treat chronic hepatitis B before it was applied to chronic hepatitis C. Interferon does facilitate the seroconversion of HBe antigen to HBe antibody, but the efficacy is rather limited. It is controversial whether interferon therapy reduces HCC development in chronic hepatitis B patients.

Lamivudine, an inhibitor of RNA-dependent DNA polymerase, effectively suppresses hepatic inflammation caused by HBV.16 The exacerbation following the appearance of resistant virus has been a difficult problem in lamivudine therapy but it can now be circumvented by novel antiviral agents, such as adefovir and entecavir. HBV-mediated hepatocarcinogenesis is believed to be associated with the integration of viral DNA into the host genome. Suppression of inflammation and regeneration may diminish the chance of DNA integration and thus the risk of HCC, although the effect remains to be confirmed in clinical trials.
Treatment of HCC

Diagnosis and treatment of HCC is detailed in other articles and will not be reiterated here. Complete removal of HCC nodules can be achieved by surgical resection or by medical ablation. Microscopic intrahepatic metastasis, which will result in early-phase recurrence, is not infrequent but the risk can be reduced by detecting HCC at an early stage. This can be facilitated by the recognition of high-risk patients. Nevertheless, recurrence is distressingly frequent after apparently curative surgery or ablation. A distinctive characteristic of HCC is the fact that the recurrence rate does not decline with time after initial treatments. Most cases of late-phase recurrence are thought to be due to metachronous multicentric, or de novo, carcinogenesis. This is quite understandable, because the remaining liver, often cirrhotic, is still at high risk of the cancer. The rate of metachronous recurrence after complete resection or ablation is estimated at as high as 20% per year, presenting an extremely high risk group.

An obvious solution to the difficulty will be liver transplantation. At least theoretically, liver transplantation provides each patient with a completely cancer-free liver with normal function. Currently, the presence of HCC per se, when extrahepatic metastasis can be ruled out, is not considered a contraindication, but an indication for liver transplantation. However, the feasibility of liver transplantation is limited worldwide by the scarcity of tissue donors. Living-related liver transplantation is an alternative choice but not always possible. Moreover, in both cadaver and living-related liver transplantation, the control of hepatitis viruses, especially HCV, is particularly difficult with postoperative administration of an immunosuppressant.

Another approach is the combined treatment of HCC and viral hepatitis. After the complete ablation of HCV-related HCC with percutaneous ethanol injection, we treated 49 patients with interferon monotherapy. A low HCV-RNA titer was an inclusion criterion, and a sustained virologic response was achieved in 14 (29%) patients. The rate of first recurrence of HCC did not differ between the interferon-treated patients and untreated controls. The recurrence was vigorously treated with ethanol ablation in each patient. The rates of second or third recurrence were different between the two groups. The interferon-treated patients as a whole had a survival rate of 68% at 5 years and 53% at 7 years, whereas untreated patients had a survival rate of 48% at 5 years and 23% at 7 years. Survival rates in sustained virologic responders were 78% at 5 years and 68% at 7 years. These results suggest that metachronous carcinogenesis was suppressed by the elimination of HCV, leading to prolonged life expectancy. Improvement in liver function was another factor contributing to the good prognosis among the responders. Today, with interferon therapies with improved efficacy, we can anticipate more favorable outcomes.

Conclusions

Prevention and treatment of HCC should consist of three levels of strategies. At the first level (prevention of hepatitis virus infection), we already have effective measures, promising a future decrease in HCC incidence. At the second level (treatment of viral hepatitis), we have recently achieved considerable improvements in interferon therapy against HCV and antiviral agents against HBV. The strategy at the third level (treatment of HCC) should include the prevention of recurrence.

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