Preface

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On behalf of the Miyakawa Memorial Research Foundation (MMRF), I am extremely pleased and deeply honored to make the opening remarks and to start the Second MMRF Meeting on Viral Hepatitis in Asia held on May 15, 2004, here in Tokyo. The carrier rate of hepatitis B virus (HBV) in Asian countries is high at 5–10% and is responsible for a high incidence of hepatocellular carcinoma (HCC), 90% of which is induced by the persistent HBV infection. Hence, there has been a pressing need to cope with this serious situation in Asia. It has become evident that, for the establishment of the HBV carrier state, not only maternal transmission, but also horizontal transmission in the infancy plays a major role. Therefore, to prevent HBV infection, all newborns receive universal vaccination by the recommendation of the World Health Organization. The vaccination has been very effective and reduced the carrier rate to less than 1% in hyperendemic countries in Asia, represented by China and Taiwan. However, this is not enough, leaving room for future improvement.

The carrier rate of HBV in Japan was 1% in the 1970s, which is much lower than that in other Asian countries. Nevertheless, the annual incidence of HCC was high during these years at 10 per 100,000 population. Of all cases of HCC, 40% were induced by HBV infection, which urged us to cope with HCC associated with HBV. As a first step, we studied how HBV spread, because prevention of *de novo* infection is most effective in dealing with

any diseases induced by bacteria and viruses. Regarding the results, it became evident that the vast majority of HBV carrier state in Japan is established by perinatal transmission from mothers with hepatitis B e antigen (HBeAg) in serum. In 1986, immunoprophylaxis was started as a national program on the babies born to carrier mothers with HBeAg, not only with hepatitis B vaccine but also with high-titered hepatitis B immune globulin; this is unique to Japan. The program has proven to be very effective in containing HBV infection in Japan, and the carrier rate in the Japanese younger than 15 years has become 0.03%.

As for the infection with hepatitis C virus (HCV), it spread widely all over the country during turmoil surrounding the termination of World War II through intravenous stimulants (e.g., methamphetamine) and transfusion with blood from commercial donors. The wide spread of HCV infection during these years manifests itself most vividly in the profile of HCV infection in the general population in Japan nowadays. The age-specific prevalence of HCV in Japan was surveyed during 1995–2000 on approximately 3.5 million first-time blood donors, conducted at the eight jurisdictions of the Japanese Red Cross Blood Center. The results of this large-scale survey are summarized in figure 1. Although the HCV carrier rate in the age group younger than 19 years is low at 0.1%, it increases sharply with age to 1.3% in the forties and jumps to 3.4% in the sixties. This profile differs

Fig. 1. Profile of HCV infection in the general population of Japan represented by the first-time blood donors. Modified from the results by Tanaka et al. [1].

Fig. 2. Deaths due to HCC increasing with time during the past 30 years in Japan. Modified from the results by Yoshizawa et al. [2].

Fig. 3. The etiology of HCC changing with time in Japan. Based on data by the Japan Association for the Study of Hepatocellular Carcinoma.

Table 1. Strategies for the treatment of chronic hepatitis C toward suppression of the development of liver cirrhosis and HCC

1	Complete clearance of HCV (sustained virological response) IFN: human lymphoblast, recombinant IFN- α_{2a} , rIFN- α_{2b} , consensus, IFN- β rIFN- α_{2b} plus ribavirin (since 2001)
2	Normalization of ALT (biochemical response) Glycyrrhizin (SNMC) Ursodeoxycholic acid Phlebotomy
3	Early diagnosis of HCC (screening every 3 or 6 months) Ultrasonography Tumor markers AFP PIVKA-II (des- γ -carboxyl prothrombin)

significantly from that in the United States reported by Dr. Miriam Alter, where the carrier rate peaks in the thirties.

We have been deeply worried that deaths due to HCC have kept increasing during the last 3 decades (fig. 2). Yearly deaths due to HCC per 100,000 population in Japan started to increase rapidly since 1975 and multiplied fourfold to reach 35 per 100,000 population in the year 1995 for men. A similar increase has occurred in women, but not to such a high extent as in men. What is responsible for such a steady increase in deaths due to HCC in Japan?

The etiology of HCC was examined in cases all over Japan, and the results since 1977 were compiled by the Japan Association for the Study of Hepatocellular Carcinoma (fig. 3). HBV has barely increased as the etiology of HCC during the past 30 years; it has been responsible for about 4 deaths per 100,000 population-year. Evidently, cases without HBV infection, which were categorized in non-A, non-B etiology, started to increase after 1975 and were responsible for the rapid gain in HCC in Japan. The mystery was solved in 1991, when a serological test for antibody to HCV became possible. In retrospect, HCV has been responsible for most increments since 1975, as we suspected without solid evidence. HCV has taken an ever increasing role in the development of HCC during the past 30 years and accounts for about 75% of deaths due to HCC at present.

Based on this background, treatment of chronic hepatitis C in Japan is required for preventing the development of HCC, using three different strategies (table 1).

The first option is the clearance of HCV infection by means of interferon (IFN) combined with ribavirin. Non-responders to this treatment and patients without indication to it are treated with Stronger Neo-Minophagen C (Minophagen Pharmaceutical Company, Ltd., Tokyo, Japan) and ursodeoxycholic acid as well as phlebotomy; they are performed to normalize serum levels of alanine aminotransferase (ALT) in patients with chronic hepatitis C with or without cirrhosis. Lastly, patients with chronic hepatitis C with or without liver cirrhosis need to be examined for HCC by ultrasonography at appropriate intervals and screened for tumor markers in serum, such as α -fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II; also known as des- γ -carboxyl prothrombin). By virtue of such close follow-ups for an early detection of tumors, the 5-year survival rate of patients who are diagnosed with HCC less than 20 mm in diameter has nowadays reached more than 70%.

Fortunately, the prevalence of HCV in most Asian countries is still much lower than that in Japan. For instance, in a study performed in collaboration with the West China University in 1996, we have not found a single person with HCV RNA in serum amongst 3,000 inhabitants of farming villages in the Chendu area of Suchen. However, occasional cases of chronic hepatitis C were found among patients who visited hospitals. Looking at countries other than China, increases in transmission of HCV through intravenous drug abuse are creating much problem in Indonesia at present.

It would be very significant and fruitful for you to take the opportunity of this meeting and discuss in depth the epidemiology, pathophysiology and as well as HCC treatment of chronic hepatitis C with the many distinguished doctors from developed countries in Asia. Let me expect to witness a big development today. Finally, I would like to extend my cordial gratitude to Schering-Plough K.K. for their generous sponsorship in holding this meeting.

References

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