Clinical Aspects of Hepatocellular Carcinoma in Japan

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Abstract

HCC in Japan has very different characteristics from that in other Asian countries. Because, among the Japanese HCC patients approximately 80% of the patients are HCV positive and they are aged over 60 years old. On the other hand, in many Asian countries HBV-positive HCC patients are dominant and their age is younger than the Japanese patients.

Early diagnosis of HCC is mainly performed by means of imaging diagnostic technique such as abdominal ultrasonography, dynamic CT, dynamic MRI and CT angiography. If small HCC less than 3 cm in diameter is found and liver function is well preserved, local ablation therapy or surgical treatment promises better than 5 years survival (over 60%). While, TAE or TACE is performed in cases of HCC larger than 3 cm in size, if liver failure is not complicated. In advanced HCC cases with multiple tumors, arterial infusion of anti-cancer drug has been applied. However, its efficacy is not estimated.

Chemoprevention is another modality for HCC. Eradication of HCV with an anti-viral agent has proven to prevent hepato-carcinogenesis. As for chemoprevention of HCC, some trials are on going in Japan.

Key words: hepatocellular carcinoma, clinical aspects

Introduction

Hepatocellular carcinoma (HCC) is currently a very common malignancy and its incidence is increasing, both in the far eastern Asian countries and in the US. Particularly, in Japan, persistent hepatitis C virus (HCV) infection is a major risk factor for the development of HCC, which is quite different from other Asian countries. Therefore, we have to recognize that HCV-associated chronic liver diseases are an extremely risky condition considering the complication of HCC.

However, the molecular mechanism of hepatocarcinogenesis in HCV infection remains unclear. Because, HCV belongs to RNA virus, and is not integrated into host hepatocyte DNA which causes the mutation. Whereas, concerning HBV, it is well known that integrated HBV genome into hepatic DNA may play an important role in hepatocarcinogenesis (1-3).

As for the mortality rate among the patients of HCC, it reached to over 30 per 100,000 population by 1995. Each year thereafter, in every year, over 30,000 patients dye of HCC. On the other hand, according to the “White Paper on the Trend of National Public Health in 2004” published by the Japanese Ministry of Health, Labor and Welfare, the mortality tends to decline gradually from 1996 in accordance with the recent progress of early detection and treatment of HCC.

In spite of the improvement in the mortality rate, there is a large number of patients with HCV-associated chronic liver diseases of over approximately 2 million that predisposes for HCC. Therefore, in order to improve the high mortality rate of HCC, we must determine epidemiological and clinical aspects of HCC in our country.

Characteristics of HCC in Japan

1. Epidemiology

Chronic infection with HCV or HBV is the major cause of HCC in Japan. Approximately 80% of Japanese HCC cases are derived from HCV-associated liver cirrhosis and chronic hepatitis, whereas the remaining less than 20% of patients are HBV positive. The frequency of HCC patients has increased rapidly since after 1980. Although it is not clear why the number of patients has increased, we must re-
As for an association with genotype of HCV and HCC, the incidence of genotype 1b is markedly high among the patients. In Japan, genotype 1b is undoubtedly the dominant type. Consequently, it is not clear whether genotype 1b plays an important role in hepatocarcinogenesis in comparison with genotypes 1a, 2a, 2b, 3 and 4.

The annual incidence of HCC from HCV positive liver cirrhosis and chronic hepatitis is 6~7% and 1~2% (4), respectively. As for hepatocarcinogenesis among the patients with HCV positive liver diseases, HCC develops frequently in cirrhotic liver, whereas among the patients with HBV positive liver diseases HCC occurs not only in the cirrhotic liver, but also in chronic hepatitis. This difference may depend on the different properties of two viruses. That is, HBV is DNA virus and its X genome inhibits activity of $p53$ known to be a suppressor oncogene (3). On the other hand, HCV known to be a RNA virus does not directly affect the host hepatic DNA. There is a report that HCV core protein enhances cell proliferation via activation of mitogen-activated protein kinase (MAPK) /extracellular signal-regulated kinase (ERK) (5-7).

The mitogen-activated protein kinase (MEK) /ERK signaling pathway is fundamental (8) in controlling cell development, proliferation and cell cycle. While, there is increasing evidence that reactive oxygen species are produced by the interaction of HCV core to host liver mitochondria and results in DNA damage (9, 10). This DNA damage may cause mutation of hepatocytes as a result of genetic change. Taken together, HCV core may be involved in hepatocarcinogenesis in some role.

The incidence of HCC is higher in male patients, as compared with females. This difference is also not clear. However, it may be depend on different expression of the aldosterone receptor between male and female patients (11). This biological characteristic has been applied to hormone therapy in HCC with Tamoxifen (12). However, its therapeutic effect has not been confirmed.

The incubation period from initial infection of HCV to outbreak of HCC is about 30 years on average. Since 1989 when the check system for serum HCV was introduced into Japan, HCV positive blood has been excluded from medical use, and thereafter nowadays the number of new patients of HCV-related liver diseases has remarkably decreased. Therefore, the incidence of HCV positive liver diseases of a young age, below 20 years old, is extremely low, as compared with those over 40 years old. The peak age among the patients with HCC has been older than 60 years old. Therefore, HCC in Japan is recognized to be a malignancy particularly in the aged (13). This is quite in contrast to the countries where are the high incidence of HBV positive HCC patients are younger age.

2. Establishment of high risk group for HCC

According to Tsukuma (14), the following factors are im-
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1. Diagnosis

Progress of the screening system of HCC has made it possible to detect it in an early stage and the advancement of treatment has improved the 5-year survival rate. At present, the 5-year survival rate of HCC in Japan is over 60% among the patients indicating the stage of liver damage A according to the Liver Cancer Study Group of Japan (15) or the stage 0 due to the Japan Integrated Staging Score (JIS) (16).

Tumor markers such as α-fetoprotein (AFP), AFP-L3, and PIVKA-II are often used for screening of HCC. However, detection of early or small HCC (less than 3.0 cm in diameter) is difficult by means of these tumor markers. While, these tumor markers are useful for the prediction of recurrence of HCC. Different from tumor markers, the imaging diagnosis using ultrasound (US), computed tomography (CT), magnetic resonance (MR) and hepatic angiography with or without CT is extremely useful for the detection of small HCC. Imaging diagnosis clearly indicates localization of HCC inside the liver. Whenever a suspected lesion is found by routine imaging diagnostic technique, angiography (with or without CT), dynamic CT or dynamic MR should be applied for confirmation of the diagnosis of HCC. A rigid check system in Japan for the early detection of HCC has made clear of the presence of borderline lesions known to be adenomatous hyperplasia or dysplasia. In general, HCC is fed by arterial blood, but borderline lesions are fed by portal blood. Consequently, in the case of hepatic angiography HCC is stained in the arterial phase with contrast medium injected via catheter placed into the hepatic artery, and also in the case of dynamic CT or MRI HCC is stained in the early phase within 30 seconds with the contrast medium injected intravenously. Combination with hepatic angiography and CT, so-called CT-angiography, is the strongest weapon for the early detection of HCC. On the contrary, in general borderline lesions are not stained those methods. Another characteristic of borderline lesions is that the size is usually less than 15 mm. However, confirmed diagnosis of a borderline lesion is only available by histological study of biopsied specimen (17).

The study group for “Guidelines for the Management of HCC Based upon EBM” (group chief: Professor M. Makuuchi, Tokyo University School of Medicine) proposed by the Minisry of Health, Labor and Welfare made an algorism for the surveillance of HCC (Fig. 1). Application of this algorism will be useful for early detection of HCC.

2. Therapy

Surgical resection should be the first choice in the therapy of HCC as well as in other solid cancers. However, HCC develops usually in the cirrhotic liver accompanied with se-
vere liver damage and therefore surgical treatment is so limited. The study group mentioned above also proposed an algorithm on the treatment of HCC (Fig. 2). The concept that surgical resection should be the first line must be correct, because the operated group has indicated a better than 5 year survival rate and good cost benefit in comparison with the patients group treated by local ablation therapy.

However, in general, patients do not want to have open surgery, even if we strongly recommend a surgical therapy in the case of small HCC developed in Child A cirrhotic liver such as liver damage A or JIS 0-1n HCC staging system. In such cases, we have applied a local ablation therapy using radio-frequency ablation (RFA). RFA is easy to operate if the operators have sufficient experience with ultrasoundography and therefore the number of cases treated by RFA is markedly increasing. But, we must pay attention to severe complications such as perforation of the gastrointestinal tract, intraperitoneal bleeding, hemobilia and liver abscess. In addition, we must note the spread of cancer cells through the inserted RFA needle into HCC due to increased pressure inside of the tumor caused by ablation. There are two types of ablation needles; one is the cool-tip type, and the other is Christmas tree like. We do not know which one is more convenient or stronger in ablation. Usually, RFA is applied to therapy of HCC in which the main tumor is less 3 cm and there are less than 3 satellite nodules.

Trans-hepatic arterial embolization (TAE) or trans-hepatic chemo-embolization (TACE) is usually performed in cases of bigger HCC over 3 cm in size. Of course, in cases that the tumor is less 3 cm in size and hypervascular, TAE or TACE is performed in combination with percutaneous ethanol injection (PEI) or RFA. TAE or TACE should be avoided in the patients whose residual hepatic function is poor, such as Child C. Otherwise, TAE or TACE in Child C makes hepatic function worse.

Arterial infusion of anti-cancer drug has been applied in the therapy of advanced cases of HCC which are not indicated for surgical treatment, local ablation and TAE or TACE. Before introduction of continuous infusion of anti-cancer drug, one shot arterial injection of the drug has been performed, but the effectiveness of this method was not clarified. Since the introduction of continuous arterial infusion, several regimes have been used as follows: 1) low dose of cisplatin and 5-fluorouracil (18), 2) low dose of cisplatin and 5-fluorouracil with leucovolin (19), 3) methotrexate, 5-fluorouracil, cisplatin and interferon-α2b (20), 4) 5-fluorouracil and subcutaneous interferon-α (21). The effectiveness of arterial infusion of chemotherapeutic agents has not been estimated in a scientific manner. Because, the subjects are all Child C stage, and the data reported are not evidence based. However, although the number of enrolled patients was not sufficient, our study showed significant prolongation of the survival period among the patients treated as compared with the control (19).

On the other hand, from the view point of the patient’s quality of life we have to carefully select the chemotherapy for each individual patient, especially in advanced case, because of longer admission and severe adverse effects due to toxicity of chemotherapeutic agents.

Chemoprevention is another method of the therapy. Almost all HCC occurs in the liver of chronic hepatitis and liver cirrhosis caused by HBV and HCV. Consequently, eradication of these hepatitis viruses with anti-viral agents may decrease a risk of HCC (22-24). In the therapy of chronic liver diseases caused by HBV and HCV, the therapy using antiviral agents, interferon and lamivudine against HBV and interferon with or without ribavirin, against HCV, should be the first choice. Of course, HCV genotype 1b which is dominant among the HCV positive patients in Japan is remarkably resistant to interferon therapy, fortunately however combination therapy with PEG-interferon and ribavirin has improved the success rate for the eradication of HCV up to 60%.

Phlebotomy improves the liver function accompanied by a decrease in the serum iron level and significantly inhibits the development of HCC, as compared with the control in whom phlebotomy was not applied (25). Although it is known whether iron radical is very toxic, there is also increasing evidence that ROS produced by infection of HCV may play an important role in hepatocarcinogenesis (9, 10). Our studies showed clearly that attachment of HCV core to hepatic mitochondria disrupts electron transport and accelerates ROS production (9). Consequently, anti-oxidant may lead to the decrease of risk of HCC (26, 27). On a different line of agents than anti-viral and anti-oxidative agents, the following two agents developed in Japan have been noted from the view points of chemoprevention of HCC: one is acyclic retinoid (28, 29), and the other is vitamin K2 (30). Although the pharmaceutical action of these drugs is not fully understood, acyclic retinoid may induce the clonal deletion due to the induction of apoptosis in premalignant lesions and vitamin K2 may act as an anti-proliferative agent (31). A clinical trial for the evaluation of these drugs is now ongoing in Japan.

We must bear in mind that HCC can be a preventable disease if we exclude HCV by anti-viral agents and directly ROS by antioxidants. Concerning acyclic retinoid and vitamin K2, we must wait for the results of the clinical trial currently underway.

Liver transplantation is another modality to relieve the patients of HCC. However, in Japan it is quite difficult to pursue liver transplantation for HCC patients even if they want it due to the shortage of donors. To date, the number of HCC patients transplanted is so limited. However, over 70% of the transplanted patients are surviving free of HCC. Liver transplantation for HCC patients should be become more available.

**Conclusion**

In this article, epidemiology of HCC in Japan and its medical practice at present are described. The mortality rate...
of the patients with HCC is ranked the 3rd in males and 4th in females among malignancies. Therefore, we, physicians, must pay attention to the characteristics of Japanese patients and possible to apply to make an effort to detect HCC in the early stages when it is possible to apply curative therapy.

References


