Chapter 1 Prevention

- **Introduction**

Eighty percent of hepatocellular carcinoma cases are caused by infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). Cases of fatty liver and nonalcoholic steatohepatitis (NASH) have recently increased, and although this may indicate a causal relationship with hepatocellular carcinoma, these complications are present in the majority of cases of cirrhosis. Therefore, inhibiting the growth of causative HBV or completely eliminating HCV may prevent hepatocarcinogenesis in patients with viral hepatitis. It is imperative that we thoroughly understand the evidence supporting the inhibition of carcinogenesis and consequently design evidence-based treatment measures. Countermeasures that were instituted in Japan in 1985 to prevent mother-to-child HBV transmission have been successful, and the number of young HBV carriers has decreased dramatically. There have also been no cases of HCV infection resulting from blood transfusion since 1992, and overall, the development of new HCV infections has become extremely limited. Moreover, primary prevention measures have continued to be successful. Ten years or more from now, HBV and HCV carriers may no longer exist in Japan, and we hope that the incidence of hepatocellular carcinoma will decrease.

Nevertheless, patients who are already infected with HBV and HCV are at risk of developing liver cancer. It is important to clearly show supporting evidence when recommending antiviral therapy for the secondary prevention of hepatocellular carcinoma in patients with chronic hepatitis or cirrhosis. There has been a rapid increase in the development of direct-acting antiviral agents against HCV, and more patients are achieving viral clearance. At this stage, evidence needs to be presented that treatment with interferon prevents hepatocarcinogenesis. It is anticipated that oral medications alone without interferon will be able to eliminate viruses; however, this will require continuous verification of the decrease in the incidence of hepatocellular carcinoma.

Treatment with nucleoside analogs prevents the progression of liver fibrosis in patients with

chronic hepatitis B infection and cirrhosis, and although this treatment may lead to a decrease in the incidence of hepatocellular carcinoma, evidence-based data must be presented. Hereafter, we are faced with the urgent task of identifying markers associated with hepatocarcinogenesis and designing countermeasures to prevent the development of hepatocellular carcinoma.
Although fatty liver has been implicated as a causative factor in hepatocellular carcinoma, no detailed evidence has been demonstrated to this date. It is an important future agenda to identify fatty liver-related risk factors for hepatocarcinogenesis and prevent hepatocellular cancer.

Section 1 Interferon Therapy

CQ1 Does interferon therapy chronic hepatitis C infection effectively prevent HCC?

Recommendation

Antiviral therapy, mainly with interferon, is recommended to prevent cancinogenesis in patients with chronic hepatitis C or compensated hepatitis C-related cirrhosis **(Grade B)**.

- **Background**

In Japan, patients with chronic hepatitis C/cirrhosis are categorized as the highest-risk group for hepatocellular carcinoma. We examined whether interferon therapy decreases carcinogenesis in patients with type C chronic liver disease.

- **Scientific Statement**

Interferon therapy decreases the risk of carcinogenesis in patients with chronic hepatitis C/compensated hepatitis C-related cirrhosis. Two meta-analyses showed that the risk of cancer development decreased significantly when interferon therapy was administered to patients with chronic hepatitis C/compensated hepatitis C-related cirrhosis (L3F005221 Level 1a; risk ratio:

0.49, L3F009212 Level 1a; risk ratio: 0.44). Miyake et al. performed a meta-analysis of three randomized controlled trials (RCTs) and six prospective cohort studies and reported that the treatment of type C chronic liver disease with interferon therapy decreased the risk ratio of carcinogenesis to 0.45 (95% confidence interval: 0.31–0.65; $p < 0.00001$). Although it is clear that the inhibitory effects on carcinogenesis are observed mainly in patients with sustained virological response (SVR), there is both positive and negative evidence regarding the efficacy of long-term low-dose peginterferon therapy in patients who are unresponsive to previous treatment with peginterferon/ribavirin combination therapy.

- **Explanation**

This revision was given a Grade B rating, similar to that in the previous edition. This is because of the fact that, of the available interferon therapies for treating advanced chronic hepatitis C/cirrhosis, two out of three RCTs on long-term low-dose peginterferon therapy for patients who were unresponsive to previous treatment with peginterferon/ribavirin combination therapy did not show a significant difference in cancer prevention. On the other hand, many reports clearly revealed that the cancer incidence decreased and survival rate increased if SVR was achieved. If the characteristics of the virus (genotype, viral load, and viral mutations) and host factors (IL-28B, etc.) are favorable, antiviral therapy, mainly interferon therapy, is recommended to proactively achieve SVR.

Using the key words “hepatocellular carcinoma,” “interferon therapy,” and “hepatitis C,” abstract forms were created from two meta-analyses and 10 original articles that examined cancer incidence rates among patients with chronic hepatitis C and cirrhosis. Of these studies, we adopted the two meta-analyses and nine original articles that included interferon nontreatment groups. In both meta-analyses, interferon administration resulted in the inhibition of hepatocellular carcinoma onset (L3F00522[1)] Level 1a, L3F00921[2)] Level 1a). These studies were conducted in patients with chronic hepatitis C and compensated hepatitis C-related cirrhosis, and there is no evidence supporting the fact that interferon inhibits carcinogenesis in patients with decompensated

hepatitis C-related cirrhosis.

In recent years, advances in antiviral therapy have brought about several changes in treatment methods, starting from conventional interferon monotherapy to peginterferon/ribavirin combination therapy and finally moving on to to direct-acting antiviral (DAA) combination therapy. On the other hand, however, many patients with type C chronic liver disease in Japan are characterized by high titers of genotype 1 virus, older age, and advanced fibrosis (i.e., intractable cases). All three RCTs on long-term low-dose peginterferon therapy in patients who were unresponsive to previous treatment with peginterferon/ribavirin combination therapy were reported in the West. The HALT-C study presented by Di Bisceglie et al. in 2008 was an RCT of 1,050 patients (517 patients in the interferon group and 533 patients in the nontreatment group; study period, 3.5 years) that demonstrated no significant difference in cancer incidence rates between patients with and without cirrhosis in both groups. The mortality rate was significantly higher among patients without cirrhosis in the peginterferon group than among those in the nontreatment group (5.0% vs. 1.9%, $p = 0.04$; L3F00375[3], Level 1b). Subsequently, however, in the extended observation period of the HALT-C study (median observation period, 6.1 years), Lok et al. reported that carcinogenesis was significantly more inhibited in the long-term low-dose peginterferon treatment group than in the control group (hazard ratio: 0.45, 95% confidence interval: 0.24–0.83; L3F00509[4], Level 1b). Nevertheless, the anticarcinogenic effects of peginterferon were not observed in patients without cirrhosis. The number of new patients with liver cancer among patients with cirrhosis is said to have increased from 53 to 88 because of the extended observation period and the inhibitory effects of peginterferon on carcinogenesis. Bruix et al. conducted a similar RCT of 626 patients with type C cirrhosis (311 in the interferon treatment group and 315 in the control group; median observation period, 2.5 years; 63 patients with carcinogenesis), and their results did not show the inhibition of carcinogenesis after long-term low-dose peginterferon therapy in patients who were unresponsive to peginterferon/ribavirin combination therapy (L3F00337[5] Level 1b). In a HALT-C study, Shiffman et al. reported that

liver disease events, including the development of hepatocellular carcinoma, were significantly inhibited in patients who experienced a ≥4 $\log_{10}$ decrease in HCV-RNA ($p = 0.003$) after peginterferon/ribavirin combination therapy during the lead-in phase. However, these results were determined to be unrelated to whether or not long-term low-dose peginterferon therapy was administered after lead-in (L3F00587[6] Level 1b). According to the above information, there is currently no solid evidence supporting the inhibitory effects of long-term low-dose peginterferon therapy on carcinogenesis in patients who are unable to achieve SVR.

Morgan et al. administered antiviral therapy that primarily included interferon to SVR patients who had achieved viral clearance and conducted a >6-year follow-up for 140 SVR patients, 309 patients who showed no response to interferon, and 77 patients who showed biochemical complete response. The hazard ratio for developing hepatocellular carcinoma was decreased to 0.19 (95% confidence interval: 0.04–0.80) in the SVR group compared with that in the nonresponder group; however, hepatocarcinogenesis could not be completely inhibited, as was evident from the development of hepatocellular carcinoma in 3 of the 140 SVR patients (L3F00529[7] Level 2b). Hirakawa et al. reported that cirrhosis, male gender, and a patient age of ≥50 years are risk factors for carcinogenesis after SVR [hazard ratio: 12.9 ($p < 0.001$), 6.45 ($p = 0.012$), and 20.2 ($p = 0.004$); L3F00414[8] Level 2b], and Hung et al. demonstrated that diabetes mellitus is a risk factor for carcinogenesis in SVR patients without cirrhosis (L3F05747[9] Level 2b).

Both studies showed a significant decrease in the incidence of cancer among groups that achieved viral clearance (L3F00427[10] Level 2b, L3F00429[11] Level 2b). Therefore, viral clearance using antiviral therapy that primarily included interferon appears to be an effective method for preventing carcinogenesis in patients with chronic hepatitis C/type C cirrhosis. Even if SVR is achieved, however, regular long-term screening for hepatocellular carcinoma is necessary in older patients and patients with cirrhosis.

- **References**

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Section 2 Liver Support Therapy

CQ2 Does liver support therapy effectively prevent HCC?

Recommendation

Intravenous administration of glycyrrhizin is recommended to prevent cancer in patients with chronic hepatitis C **(Grade B)**.

In some patients, phlebotomy and an iron-limited diet can effectively prevent cancer in patients with active chronic hepatitis C and advanced fibrosis who are difficult to treat with antiviral therapy or are contraindicated for the same **(Grade C1)**.

- **Background**

Carcinogenesis from chronic hepatitis is thought to occur because of persistent inflammation in the liver caused by viral hepatitis and the associated necrosis and regeneration of tissue. Inhibition of liver inflammation was examined to determine whether it can prevent hepatocarcinogenesis. Glycyrrhizin has anti-inflammatory effects, inhibits liver inflammation, and decreases hepatic enzyme levels. Sho-saiko-to is a Chinese herbal medicine composed of seven types of medicinal herbs, and it is believed to protect the plasma membrane, exert anti-inflammatory effects, increase blood flow to the liver, and promote liver regeneration. These two drugs have been widely administered in Japan for liver protection; however, sho-saiko-to has not been recommended in these guidelines, as is explained in the Explanation section. Furthermore, because hepatic iron deposition reportedly leads to inflammation of the liver and is associated with carcinogenesis, there is more focus on phlebotomy and iron-limited diets at this time.

- **Scientific Statement**

Intravenous administration of glycyrrhizin in patients with chronic hepatitis C decreases the risk of hepatocarcinogenesis (odds ratio: 0.40, $p = 0.044$). Glycyrrhizin decreases the risk of hepatocarcinogenesis in patients with chronic hepatitis C/cirrhosis who are unresponsive to interferon therapy (odds ratio: 0.49, $p = 0.014$). An RCT studied sho-saiko-to in 260 patients with liver cirrhosis in the Osaka area, and carcinogenesis was observed in 23 of 130 patients in the treatment group and 33 of 130 patients in the nontreatment group over a mean observation period of 41 months. Although treatment with sho-saiko-to decreased the cancer incidence rate, the decrease was not significant ($p = 0.071$). When analysis was limited to HBs antigen-negative patients, the 5-year cancer incidence rate decreased from 39% to 22% ($p = 0.024$) after treatment with sho-saiko-to, and the 5-year survival rate improved from 60% to 76% ($p = 0.043$). Patients with chronic hepatitis C and advanced fibrosis whose transaminase levels can be decreased by phlebotomy and iron-limited diets responded with decreased 5- and 10-year cancer incidence rates compared with the nontreatment group (odds ratio: 0.57, $p = 0.0337$).

- **Explanation**

"Glycyrrhizin" and "liver tumors" were used as key words in a search of the literature. No RCTs were found; however, two retrospective studies were adopted. Arase et al. conducted a retrospective cohort study in patients with noncirrhotic chronic hepatitis C, where 84 patients were treated with glycyrrhizin and 109 patients were not treated. The results after risk factor adjustment demonstrated that the risk of hepatocarcinogenesis was decreased with the intravenous injection of glycyrrhizin (odds ratio: 0.40, 95% confidence interval: 0.16–0.99, p = 0.044; LF02395[1)] Level 2b). Ikeda et al. performed a retrospective cohort study in chronic hepatitis C/cirrhosis patients who were unresponsive to interferon therapy, where 244 patients were administered glycyrrhizin and 102 were not. The results after risk factor adjustment showed that intravenous administration of glycyrrhizin decreased the risk of hepatocarcinogenesis (odds ratio: 0.49, 95% confidence interval: 0.27–0.86, p = 0.014; LF10359[2)] Level 2b). Although the data were released from the same institution, they were adopted as separate evidence because of different study populations and periods.

"Sho-saiko-to" and "liver tumors" were used as key words in a literature search, and one document was adopted (LF02557[3)]Level 1b). As stated above, administration of sho-saiko-to may inhibit carcinogenesis in patients with cirrhosis, but the results in this study were not statistically significant. However, when analyses were limited to HBs antigen-negative patients, results were favorable in that both carcinogenesis and prognosis were improved. The study was performed in 1985, before HCV was discovered. Considering the fact that epidemiological statistics later revealed that the majority of other patients with HBs antigen-negative cirrhosis originated from HCV, it appears highly possible that sho-saiko-to will inhibit carcinogenesis from type C cirrhosis. Sho-saiko-to is not recommended, however, because the treatment of cirrhosis with sho-saiko-to is contraindicated in Japan; moreover, no new evidence has been reported.

"Phlebotomy" and "liver tumors" were used as key words in a literature search, and one document was adopted. Kato et al. used phlebotomy and iron-limited diets to treat 35 patients with active

chronic hepatitis C and advanced fibrosis who were difficult to treat with interferon therapy or unresponsive to the same. When the cumulative cancer incidence in the 35 patients was compared with that in 40 untreated patients, it was demonstrated that the 5-year and 10-year cancer incidence rates decreased in the former group compared with those in the latter group (odds ratio: 0.57, p = 0.0337; L3F05749[4] Level 2b), while the former group maintained an alanine aminotransferase (ALT) level of 60 IU/mL.

- **References**

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CQ3 Does antiviral therapy against chronic hepatitis B infection effectively prevent HCC?

Recommendation

Nucleoside analogs are recommended to prevent cancer in patients with HBV-DNA-positive, compensated HBV cirrhosis **(Grade A)**.

Interferon therapy is recommended in some patients with chronic hepatitis B **(Grade C1)**.

- **Background**

Administration of nucleoside analogs and interferon for type B chronic liver disease inhibits the proliferation of HBV, prevents inflammation, and resolves liver fibrosis. Therefore, we examined whether antiviral therapy decreased carcinogenesis in patients with chronic hepatitis B.

- **Scientific Statement**

In one meta-analysis, nucleoside analog treatment of chronic hepatitis B/cirrhosis decreased the risk of carcinogenesis by 78% (risk ratio: 0.22, 95% confidence interval: 0.10–0.50; L3F00598[1)] Level 1a). A retrospective cohort study showed that the cumulative cancer incidence was decreased ($p = 0.005$) in patients with compensated hepatitis B cirrhosis who successfully responded to oral nucleoside analog treatment to inhibit viral proliferation (lamivudine) compared with that in the control group (L3F00386[2)] Level 2b). At present, the first-choice nucleoside analog in Japan is entecavir. According to Yokosuka et al. (L3H00053[3)] Level 2b), viral proliferation is effectively inhibited because the 3-year probability of developing resistance to the virus is 3.3% and the inhibitory effect of HBV-DNA (HBV-DNA < 400 copies/mL) is 83% at 96 weeks. With regard to interferon treatment, three meta-analyses reported the inhibition of carcinogenesis; however, these effects were not observed in one meta-analysis. Race, positive HBe antigen, and cirrhosis strongly affect the inhibitory effects of interferon therapy; therefore, a universal inhibitory effect on carcinogenesis is yet to be demonstrated.

- **Explanation**

Administration of nucleoside analogs for HBV-DNA-positive compensated hepatitis B cirrhosis was a Grade B recommendation in the previous guidelines; however, it is considered a Grade A recommendation in this edition. Although four meta-analyses of interferon therapy were reported and adopted for analysis, inhibition of carcinogenesis was not universal, and the recommendation level was determined to be Grade C1.

In Japan, entecavir is the first drug of choice among nucleoside analogs; however, no reports regarding its anticarcinogenic effects were found within the time frame of our search. As a result, we adopted one meta-analysis of lamivudine (L3F00598[1)] Level 1a) and one retrospective cohort study. Eun et al. compared patients with type B chronic liver disease treated with lamivudine with a historical control group and demonstrated that carcinogenesis was inhibited in patients with compensated cirrhosis and suppression of HBV-DNA to <141,500 copies/mL after the oral administration of lamivudine (L3F00386[2)] Level 2b). In this study, regardless of the presence or absence of treatment effects from lamivudine, there was no significant difference in cancer incidence rates between patients with decompensated cirrhosis and those without. Papatheodoridis et al. reported on a follow-up study of lamivudine treatment in patients with HBe antigen-positive type B chronic liver disease and determined that virological suppression is not a factor in carcinogenesis (L3F00775[4)] Level 4). This study, however, lacked a control group, and all 818 patients were administered lamivudine. Factors related to carcinogenesis in patients consuming oral nucleoside analogs were age, gender, and presence or absence of cirrhosis.

Four meta-analyses on interferon were adopted. Miyake et al. confirmed that interferon therapy inhibited carcinogenesis in patients with chronic hepatitis B (risk difference: −5.0%, 95% confidence interval: −9.4 to −0.5, p = 0.028). Nevertheless, the treatment effects of interferon therapy can vary with race and HBe antigen status, and the anticarcinogenic effects are high, particularly among Asian patients with HBe antigen-positive chronic hepatitis B (L3F00523[5)] Level 1a). Sung et al. also reported carcinogenesis inhibition with interferon (risk ratio: 0.66, 95% confidence interval: 0.48–0.89), with treatment being particularly useful during the early stages of cirrhosis (L3F00598[1)] Level 1a). Zhang et al. conducted a meta-analysis of HBV and HCV in order to evaluate the anticarcinogenic effects of interferon in patients with chronic virus infections. Although it has been concluded that interferon does not inhibit carcinogenesis in patients with HBV infection, the only two articles on HBV published in 1999 were adopted (L3F00921[6)] Level 1a). Yang et al. conducted a meta-analysis of 11 articles including a total of 2,082 patients

(observation period, 4–7 years) and concluded that interferon therapy significantly inhibits carcinogenesis (risk ratio: 0.59, 95% confidence interval: 0.43–0.81, $p = 0.001$, $p < 0.05$; L3F00652[7] Level 1a). Shamliyan et al. systematically reviewed antiviral therapies for chronic hepatitis B and observed no significant differences in carcinogenesis inhibition between lamivudine, interferon α2b, long-term adefovir, and interferon/steroid combination therapy. Because these results were derived from only four reports, these findings were excluded in this edition (L3F05742[8] Level 1a).

Antiviral therapies for chronic hepatitis B have undergone major changes in standard therapy, from the age of lamivudine, studies on which were adopted for meta-analysis in this study, and conventional interferon α to that of entecavir and peginterferon. We hope to see more large-scale RCTs and cohort studies in the future, and it is further expected that the anticarcinogenic effects of new antiviral therapies will be verified by meta-analysis based on those studies.

- **References**

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