Chapter 3:

Prevention

● Introduction

HCC rarely occurs in the otherwise healthy liver but occurs frequently in the presence of viral hepatitis, alcoholic liver disease, and more recently, fatty liver disease. This also implies that unlike other cancers, HCC can be prevented to some extent. To establish effective preventive measures, it is essential to identify patients at high risk for liver cancer and research is currently underway to discover novel biomarkers besides viral hepatitis.

The most notable recent advance is the development of antiviral therapy against HCV. SVR is achieved in almost all patients after 12-week administration of direct acting antivirals (DAA). The probability of SVR is extremely high when DAA is administered after screening for comorbid disease and testing for preexisting drug-resistance mutations. However, despite the suppressed development of HCC after achieving SVR and improved life expectancy, the problem associated with DAA therapy, including in combination with interferon, is that there is so far no long-term observational study that involved patients treated with DAAs only. This is an important issue to address in the future.

In Japan, the incidence of liver cancer associated with HBV infection has not decreased. This has resulted in various measures against HBV infection, including a review of indications for nucleos(t)ide analogue treatment and the establishment of suppressive measures against liver cancer. It is necessary to accumulate more evidence in the future. Furthermore, novel drugs are needed to prevent adverse events in the kidneys and bone due to long-term administration of nucleos(t)ide analogues.

The incidence of HCC associated with alcoholic liver disease of unknown etiology and fatty liver has been increasing in recent years, but adequate surveillance has not been performed because the risk factors are unclear. For this reason, many HCCs are already advanced when detected. Also, the lack of studies with high-quality evidence for prevention of liver cancer meanswe need to identify new biomarkers for HCCs of unknown etiology and explore effective preventive measures against liver cancers by following up patients. However, prospective studies are challenging to conduct, so the current need is for detailed epidemiological studies involving a large number of patients.

Because the development of HCC after hepatitis virus eradication is a major concern, it is important to establish effective preventive measures against HCC by accumulating more evidence with continued follow-up of patients with HBV infection.

CQ17 What treatment modalities are recommended as preventive measures against liver cancer associated with chronic hepatitis B liver disease?

Recommendation

Strong recommendation: Nucleos(t)ide analogues are recommended as a preventive measure against liver cancer in patients with type B hepatitis positive for hepatitis B virus DNA and cirrhosis.

■ Background

Treatment with nucleos(t)ide analogues and interferon suppresses the growth of HBV and reduces liver inflammation in patients with chronic hepatitis B liver disease. Here, we investigated the validity of antiviral therapy to be recommended as a preventive measure against liver cancer.

■ Scientific Statement

This CQ was established based on CQ3 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 95 articles. This was narrowed down to 18 in the first screening and to 11 in the second screening based on the following inclusion criteria: studies with control groups and the incidence of HCC as the primary endpoint. A total of 17 articles are cited for CQ17: the 11 articles extracted here, 5 of the 8 articles cited in the third edition, and 1 article on an RCT[1] that was hand-searched from the articles published before the release of the the third edition.

A meta-analysis showed that nucleos(t)ide analogues reduce the risk of developing HCC by 78% in patients with chronic hepatitis B and cirrhosis (risk ratio, 0.22; 95% CI, 0.10-0.50)[2]. A retrospective cohort study found that the administration of nucleos(t)ide analogues (lamivudine, entecavir, and tenofovir) reduced the cumulative incidence of HCC among patients with hepatitis B compared with controls[3–11]. Entecavir and tenofovir are currently first-choice nucleos(t)ide analogues in Japan. Yokosuka et al. reported the appearance of resistant virus was 3.3% during 3-year administration of entecavir, and at week 96, the level of HBV-DNA was < 400 copies/mL in 83% of the patients, demonstrating that entecavir effectively suppresses viral growth[12]. As for interferon, 3 of 4 meta-analyses have reported that it suppresses HCC development, with its effect influenced by factors such as race, HBe antigen (HBe-Ag) status, and cirrhosis. At present, there is insufficient data to state that interferon unequivocally suppresses HCC development.

To date, only one RCT that involved the use of lamivudine has shown that nucleos(t)ide analogues suppress the development of liver cancer[1]. Similarly, only one meta-analysis evaluated the effect of lamivudine[2], and this article is cited in the current Guidelines, as it was in the third edition. However, due to the issue of drug resistance, lamivudine is currently not a drug of first choice in Japan. Regarding entecavir, the literature search extracted 5 studies that compared the incidence of HCC between entecavir and untreated groups, including a retrospective cohort study by Wong et al. (n = 1,870) where entecavir suppressed the incidence of HCC only in patients with cirrhosis (risk ratio, 0.55; 95% CI, 0.31-0.99)[6]. In contrast, Hosaka et al. showed that entecavir suppressed HCC development by analyzing all patients, including those with and without cirrhosis (hazard ratio, 0.37;

95% CI, 0.09-0.55; p = 0.03)[4]. Further investigation is needed to verify that nucleos(t)ide analogues suppress HCC development in patients with cirrhosis as well as in patients with chronic hepatitis. The JSH Clinical Practice Guidelines for Chronic Hepatitis B currently recommends anti-therapy with nucleos(t)ide analogues depending on (1) histological stage, (2) ALT level, and (3) HBV-DNA level, which suggests that nucleos(t)ide analogues are not always administered to hepatitis B patients as a preventive measure for HCC. In a retrospective cohort study of entecavir (n = 2,000) and lamivudine (n = 3,347), entecavir significantly decreased the risk of death and transplantation (hazard ratio, 0.49; 95% CI, 0.38-0.64), with no significant difference in the incidence of HCC between the 2 nucleos(t)ide analogues (hazard ratio, 1.08; 95% CI, 0.80-1.27)[13]. In another study of entecavir and lamivudine, multivariate analysis identified age and cirrhosis as significant risk factors, and there was no significant difference in the incidence of HCC between the two analogs[14]. The anti-oncogenic activity of tenofovir was investigated in patients with chronic hepatitis B by calculating the risk of HCC using the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) model[10], which estimates the incidence of HCC based on several factors. The results showed that administration of tenofovir reduced the incidence of HCC in the non-cirrhosis group but not in the cirrhosis group. Further study, especially on a large-scale, is needed to elucidate the effect of tenofovir.

As indicated above, nucleos(t)ide analogue treatment effectively suppresses the incidence of HCC. However, because HCC does occur despite this therapy, it is important to perform surveillance for HCC even in patients undergoing nucleos(t)ide analogue treatment.

■ Explanation

The third edition cites 4 meta-analyses of the effect of interferon therapy. The most recent literature search extracted a matching study showing the superiority of interferon over nucleos(t)ide analogues in preventing HCC[15], but this article was not used to grade the recommendation due to the lack of definite anti-oncogenic effect.

No additional meta-analyses on the effect of interferon were extracted in the most recent literature search and 3 meta-analyses cited in the third edition are cited in the current Guidelines as well. Miyake et al. reported that interferon therapy suppresses the incidence of HCC in patients with chronic hepatitis B (risk difference, –5.0%; 95% CI, –9.4-0.5; p = 0.028), but response to interferon therapy varies by race or HBe-Ag status. For example, the anti-oncogenic activity of interferon is particularly high among Asians with HBe-Ag-positive chronic hepatitis B[16]. Sung et al. also reported the suppression of HCC by interferon (risk ratio, 0.66; 95% CI, 0.48-0.89), and interferon was particularly useful in the early stage of cirrhosis[2]. Yang et al. performed a meta-analysis of 11 studies involving 2,082 patients (observation period, 4-7 years) and concluded that interferon therapy significantly suppresses HCC (risk ratio, 0.59; 95% CI, 0.43-0.81; p = 0.001, p < 0.05)[17]. It should

be noted that cirrhosis is not an indication for interferon therapy and that there is currently insufficient evidence to support the anti-oncogenic effect of interferon.

Before and after the publication of the third edition, strong evidence was reported for chronic hepatits B patients that the administration of nucleos(t)ide analogues suppresses HCC development. In the future, studies are needed to verify the effect of newer drugs such as tenofovir and tenofovir alafenamide. As with the third edition, the Revision Committee has unanimously decided to strongly recommend treatment with nucleos(t)ide analogues as a preventive measure against liver cancer associated with chronic hepatitis B liver disease.

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CQ18 What treatment modalities are recommended as preventive measures against liver cancer associated with chronic hepatitis C liver disease?

Recommendation

Strong recommendation: Antiviral therapy for the eradication of hepatitis C virus is recommended as a preventive measure against liver cancer in patients with chronic hepatitis C and compensated cirrhosis type C.

■ Background

Chronic hepatitis C and cirrhosis type C with a high risk of liver cancer prevail in Japan. Here, we investigated the suppression of liver cancer by antiviral therapy in patients with chronic hepatitis C liver disease.

■ Scientific Statement

This CQ was established based on CQ1 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 383 articles. This was narrowed down to 25 in the first screening and 15 in the second screening based on the following inclusion criterion of studies with the incidence of HCC as

the primary endpoint. A total of 25 articles, including the 10 articles from the third edition, are cited for CQ18.

Interferon therapy significantly decreases the risk of HCC in patients with chronic hepatitis C and compensated cirrhosis type C, as shown in 3 meta-analyses[1–3]. Miyake et al. conducted a meta-analysis of 3 RCTs and 6 prospective cohort studies and found that interferon therapy for chronic hepatitis C liver disease reduces the incidence of HCC (risk ratio, 0.45; 95% CI, 0.31-0.65; $p < 0.00001$)[1]. Messori et al. performed a meta-analysis of 25 observational studies and reported that the incidence of HCC was suppressed significantly in sustained virologic (SV) responders compared with non-SV responders[3]. Maruoka et al. conducted a study using a non-treated group as the reference group and demonstrated that interferon therapy significantly decreased the risk of HCC (hazard ratio, 0.139; 95% CI, 0.046-0.422; $p = 0.001$) and overall mortality (hazard ratio, 0.173; 95% CI, 0.075-0.402; $p < 0.001$) in SV responders[4]. Moreover, the risk of developing HCC significantly decreased after antiviral therapy and achieving virus seronegative status in SV responders compared with non-SV responders[5–20]. In a study of 2,659 patients with chronic hepatitis C who received interferon therapy, Oze et al. identified age, sex, and platelet count as pre-treatment predictive factors for HCC and SVR as a pretreatment factor that significantly reduces the risk of HCC (hazard ratio, 0.368; 95% CI, 0.183-0.737; $p = 0.005$)[17]. When pre-treatment and post-treatment factors are combined, age and AFP $\geq$ 5 ng/mL (hazard ratio, 8.096; 95% CI, 2.738-23.942; $p < 0.001$) are the risk factors for HCC. In a study conducted by Asahina et al., post-treatment AFP levels (hazard ratio, 1.06; 95% CI, 1.02-1.10; $p = 0.007$) and non-SVR (hazard ratio, 1.58; 95% CI, 1.01 – 2.48; $p = 0.044$) were predictive factors for HCC, in addition to age, male sex, and severe liver fibrosis (F3-4)[11].

Two RCTs of low-dose peginterferon maintenance therapy for HCV patients unresponsive to combination therapy with peginterferon + ribavirin were conducted in the United States and Europe. By extending the post-treatment follow-up period (median, 6.1 years) of patients who did not achieve SVR after therapy with peginterferon + ribavirin in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) study, Lok et al. showed that, compared with the control group, low-dose peginterferon maintenance therapy significantly suppressed the incidence of HCC in patients with cirrhosis (hazard ratio, 0.45; 95% CI, 0.24-0.83) but not in those without cirrhosis[21]. In a similar RCT (median observation period, 2.5 years) involving 626 patients with cirrhosis type C (311 in the interferon group, 315 in the control group; 63 definitively developed HCC), Bruix et al. reported that there was no observed beneficial effect of low-dose peginterferon maintenance therapy as a preventive measure for HCC in HCV patients unresponsive to combination therapy with peginterferon + ribavirin[22]. Two cohort studies also investigated the effect of low-dose peginterferon maintenance therapy. Both studies, one by Takeyasu et al. ($n = 494$)[23] and the other by Izumi et al. ($n = 594$)[24], showed that peginterferon therapy suppresses the incidence of HCC. Shiffman et al.

analyzed patients treated with combination therapy with peginterferon + ribavirin during the lead-in phase of the HALT-C study and found that patients with ≥ 4 $\log_{10}$ decline in serum HCV RNA had a significantly lower incidence of liver cancer and fewer hepatic adverse events ($p = 0.003$) regardless of their receiving low-dose peginterferon maintenance therapy after combination therapy with peginterferon + ribavirin[25].

■ Explanation

The strength of recommendation was B in the third edition, but the current Guidelines strongly recommend antiviral therapy for the eradication of HCV. As stated in the third edition, in many other studies, SV responders have a lower incidence of liver cancer and a higher survival rate. Therefore, antiviral therapy should be performed to achieve SVR consiering host factors (e.g., IL-28B) and viral factors (e.g., genotype, viral load, and gene mutations).

It should be noted that the studies mentioned above evaluated patients with chronic hepatitis C and compensated cirrhosis type C, and at present, there is no evidence to confirm that interferon suppresses the incidence of liver cancer in patients with decompensated cirrhosis type C.

Recent advances in antiviral therapy have shifted the mainstay of treatment for type C liver disease toward interferon-free DAA therapy. For now, there is insufficient evidence is available to verify that DAA therapy suppresses the development of liver cancer*. Nevertheless, the Revision Committee has decided to recommend antiviral therapy of any type based on extrapolation from the interferon-based evidence that the incidence of liver cancer decreases among SV responders.

However, because some patients still develop liver cancer after achieving SVR, long-term surveillance for HCC should be continued even among SV responders, especially when they are elderly or have cirrhosis or high AFP levels. Low-dose peginterferon maintenance therapy is currently not recommended for non-SV responders due to the lack of consistent evidence that this therapy indeed suppresses the incidence of liver cancer.

* Note that the literature searched for the current Guidelines involved articles published before July 2016. Many articles discussing this issue have been published since the Japanese version of the current Guidelines were released.

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CQ19 What preventive measures are recommended for liver cancer associated with viral or nonviral chronic liver disease?

Recommendations

Weak recommendation: Coffee consumption may decrease the risk of liver cancer.

Weak recommendation: Consumption of polyunsaturated fatty acids (PUFAs) may decrease the risk of HCC.

■ Background

This new CQ was established based on CQ2 “Does liver support therapy effectively prevent HCC?” in the third edition. In recent years, the incidence of liver cancer has been increasing in patients with non-B and non-C hepatitis, drawing attention to the prevention of liver cancer associated with

nonviral hepatitis. However, because many studies include patients with viral liver disease, we investigated preventive measures for liver cancer for both viral and non-viral chronic liver disease.

■ Scientific Statement

A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 284 articles. This was narrowed down to 10 in the first screening and to 3 in the second screening using the keyword "prevention of HCC". In the third edition, liver support therapy, with an emphasis on glycyrrhizin preparations, for HCV-related liver disease was a grade B recommendation. However, today, DAA therapy plays a central role in the prevention of HCC and has reduced the clinical prospects of glycyrrhizin. Accordingly, 4 related articles cited in the third edition were excluded from the current version.

A cross-sectional study has shown the association between intake of ≥ 600 mL coffee and a lower risk of liver cancer (risk ratio, 0.25; 95% CI, 0.011-0.62)[1]. In a large-scale study, intake of PUFAs reduced the incidence of HCC in a dose-dependent manner[2]. The study, which divided participants into 5 groups based on administration of different amounts of PUFAs (the lowest, 9.6 g/day, which was set at 1 in analysis; the highest, 70.6 g/day), demonstrated dose-dependent suppression of HCC by PUFAs (highest group: hazard ratio, 0.64; 95% CI, 0.42-0.96; p = 0.03). A similar study with eicosapentaenoic acid (EPA) alone generated comparable results (highest group: hazard ratio, 0.56; 95% CI, 0.36-0.85), suggesting the significance of EPA compared with different PUFAs. However, the significance of EPA over other PUFAs disappeared after adjusting for HBV/HCV infection. Another study of dietary habit (in this case, the Mediterranean diet) was published in Europe and showed an association between higher adherence scores and lower incidence of HCC[3].

■ Explanation

Several epidemiological studies have reported the association between coffee intake and a lower incidence of HCC as well as other cancers. A cross-sectional study that reported an association between coffee intake and risk of HCC, which was extracted in the most recent literature search, is included in the current edition. Also, multiple studies have reported the utility of metformin for the treatment of diabetes[4–6] and statins for the treatment of dyslipidemia[7–9] as preventive measures for liver cancer, 4 of which are epidemiological studies that used the Taiwan National Health Insurance Research Database. Although application is limited to patients with diabetes or dyslipidemia, the administration of metformin and statin likely decreases the risk of HCC. Furthermore, Kawaguchi et al. performed a prospective multicenter study of branched-chain amino acids (BCAA)[10]. Significant differences were observed between the BCAA and no-BCAA groups in the levels of albumin, ammonium, and ferritin, the ratio of BCAA to tyrosine, and Child-Pugh scores. However,

multivariate Cox regression analysis and Fine–Gray model analysis revealed that BCAA intake is significantly correlated with the incidence of liver cancer (risk ratio, 0.45; 95% CI, 0.24-0.88; p = 0.019) and overall death (risk ratio, 0.009; 95% CI, 0.0002-0.365; p = 0.015).

Unlike for virus-related liver disease, interventions for nonviral liver deiseaseare not clearly defined. In the future, prospective studies are needed to investigate the anti-oncogenic effect of treatment modalities for nonalcoholic steatohepatitis (NASH), the major cause of nonviral liver disease.

After careful consideration, the Revision Committee decided to recommend the consumption of coffee and PUFAs for CQ19, which was then established as a new CQ about the prevention of liver cancer. The recommendation is rated weak because the evidence was gathered from epidemiological studies, and not comparative or controlled studies. Metformin, statin, and BCAA are described in the Explanation section but are not recommended in the current version because the criteria for subject inclusion in these studies were limited.

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