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Anti-viral therapy to reduce recurrence and improve survival in hepatitis B virus-related hepatocellular carcinoma

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improved the survival rate of patients with hepatocellular carcinoma (HCC). However, hepatitis B virus (HBV)-related HCC has a much higher recurrence rate. In this article, we describe strategies for reducing recurrent HCC using anti-viral therapy for HBV infection.

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Abstract

Hepatocellular carcinoma (HCC) is the most common malignancy and the third leading cause of cancer death worldwide. Chronic infection with hepatitis B virus (HBV) and hepatitis C virus accounts for approximately 75%-80% of HCC cases worldwide. In particular, chronic HBV infection is a predominant risk factor for HCC in Asia and Africa. Hepatic resection and radiofrequency ablation are increasingly used for the curative treatment of HCC, and good local control can be achieved. However, the high rate of recurrence is a major obstacle to improving prognosis. A high viral load of HBV DNA is the most important correctable risk factor for recurrence. Furthermore, interferon and/or nucleotide analogues may decrease HBV DNA. Therefore, these drugs may decrease recurrence. In this article, treatment strategies for HBV-related HCC are described in order to reduce recurrence and improve survival.

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Key words: Hepatocellular carcinoma; Hepatitis B virus; Recurrence; Nucleotide analogues; Interferon

Core tip: Recent advances in treatment modalities have

INTRODUCTION

Hepatic resection or liver transplantation provide a complete curative treatment for hepatocellular carcinoma (HCC)^[1,2]. In addition, regional ablation therapy including radiofrequency ablation (RFA) is now increasingly used for the curative treatment of HCC, and good local control can be achieved^[3-5]. However, these techniques are unsatisfactory due to a high post-treatment recurrence rate^[6]. It was reported that up to 70% of patients relapse within 5 years after curative treatment^[7].

This high rate of recurrence is a major obstacle to improving prognosis. Therefore, antiviral and anti-inflammatory therapies both before and after curative treatment may be crucial in preventing HCC recurrence and improving survival. Current approved medications for chronic hepatitis B treatment are interferon- α (IFN α) and nucleotide analogues (NAs), including lamivudine (LVD), entecavir (ETV), tenofovir disoproxil fumarate, adefovir-dipivoxil (ADV), and telbivudine^[8]. However, despite curative treatment of HCC, the 5-year recurrence rate remains high, at 70%-80%^[9]. The mechanisms of HCC recurrence differ greatly from those of other carcinomas in terms of the high rate of intrahepatic metastases and multicentric carcinogenesis against a background

of viral liver disease. Whether antiviral therapy after treatment of HCC can prevent recurrences is thus an important issue. Interferon (IFN) therapy in hepatitis C virus (HCV)-related HCC has been reported to reduce recurrence rates and contribute to survival, and its significance in preventing secondary carcinogenesis^[10-14] including improvement of hepatic functional reserve^[15] has been established.

The treatment of hepatitis B virus (HBV)-related HCC has centered on nucleic acid analogues to reduce viral load and inactivate hepatitis, however, treatment with IFN, similar to that in type C hepatitis, has recently attracted attention. Nucleic acid analogues and IFN may act together, but therapeutic strategies for preventing secondary carcinogenesis after treatment of HBV-related HCC remain unclear. This paper reviews the clinical evidence regarding treatment from the perspective of preventing secondary carcinogenesis, including reducing recurrence rates and improving prognosis after curative treatment of HBV-related HCC.

ROLE AND MECHANISM OF HBV DNA LOAD IN RECURRENT HCC

The mechanism of hepatocarcinogenesis by HBV includes direct malignant transformation and other indirect effects. With regard to direct malignant transformation, HBV gene integration into the host hepatocyte genome causes changes in host gene expression and properties, facilitating hepatocarcinogenesis^[16,17].

Hence, as an indirect effect, persistent infection by HBV leads to hepatocyte destruction and regeneration, increasing genetic instability^[18]. Epidemiological studies have examined differences in carcinogenesis due to HBV DNA load^[19], however, the mechanisms by which HBV DNA load causes differences in malignant transformation remain unclear.

HBV DNA load has been shown to play a role in carcinogenesis in patients with type B chronic liver disease, and more recently, HBV DNA load has also been reported to be involved in recurrence after curative treatment of HCC.

In a retrospective study of 72 patients with hepatic resection for HBV-related HCC, Hung *et al*^[20] reported that patients with a high serum HBV DNA load at the time of tumor resection showed a significantly higher recurrence rate, compared to patients with a low viral load. Multivariate analysis showed that a high HBV DNA load, alpha-fetoprotein level, tumor size, and age were factors contributing to recurrence. Xia *et al*^[21] reported that high serum hyaluronic acid and HBV viral load are the main prognostic factors of local recurrence after complete radiofrequency ablation of hepatitis B-related small HCC.

Because HBV DNA load changes with the administration of antiviral drugs, patients with a high viral load at the time of HCC treatment who receive antiviral drugs subsequently show differences in HBV DNA load com-

pared to those who do not receive such treatment. Kim *et al*^[22] analyzed the patients excluded from antiviral drug therapy. After the patients treated with antiviral drugs were excluded, recurrence-free survival rates in a total of 157 patients with HBV-related HCC who underwent hepatic resection were compared between 89 patients with a persistently low HBV DNA load and 68 patients with a persistently high viral load. Recurrence-free survival rates were better in the persistently low HBV DNA load group compared to the high level group.

MECHANISM OF ANTIVIRAL DRUGS IN PREVENTING RECURRENT HCC

NAs preparations

The direct antitumor activity of nucleotide analogues has not been reported. Lamivudine has no inhibitory effects on integrated HBV DNA, thus there is no suppressive effect on de novo carcinogenesis due to HBV gene integration into the host genome^[23,24].

Considering that HBV DNA load is related to HCC recurrence, the prevention of recurrence by antiviral drugs, rather than direct antitumor effects, is due to a reduction in HBV DNA load which improves hepatocyte destruction and regeneration and reduces genetic instability, thus decreasing HCC recurrence rates. Hosaka *et al*^[25] reported that HBV core-related antigen levels were independent risk factors for HCC recurrence. In addition, Chuma *et al*^[26] reported that recurrence was significantly lower in patients who received lamivudine before the development of HCC.

In a retrospective study by Kubo *et al*^[27] of 24 patients with HBV-related HCC who underwent liver resection, a difference in recurrence-free survival rates was seen between 14 patients who received lamivudine and 10 patients who did not. Multivariate analysis also showed that lack of antiviral therapy and multiple tumors were factors related to recurrence-free survival rates.

In another retrospective study of 49 patients who underwent curative treatment for HBV-related HCC (liver resection, 31 patients; RFA, 18 patients), Kuzuya *et al*^[28] examined cumulative recurrence rates of HCC in 16 patients who received lamivudine and 33 patients who did not. There was no significant difference between the two groups. Although there was no significant difference in HCC recurrence rates, hepatic functional reserve was improved and survival was better in the lamivudine group. In the lamivudine group, hepatic functional reserve was significantly better at the time of HCC recurrence, a higher percentage of patients were able to undergo curative treatment, and prognosis tended to be better (Table 1).

Other studies^[29,30] have reported significantly larger remnant liver volume and better prognosis after liver resection in lamivudine-treated groups, and that lamivudine improves liver function and reduces deaths due to liver failure. Lamivudine after treatment of HCC may not prevent cancer recurrence, but may contribute to an improved prognosis by maintaining hepatic functional

Table 1 Studies in which Nucleoside analogues were administered after treatment for hepatitis B virus-related hepatocellular carcinoma

Authors	Treated vs Untreated	Treatment	Observation time	HCC Tx	Recurrence	Survival
Kubo <i>et al</i> ^[27]	14 vs 10	LVD	1117 d (median)	Ope	NA	Tumor-free survival (P = 0.0086)
Kuzuya <i>et al</i> ^[28]	16 vs 33	LVD	38.0 mo vs 32.6 mo (median)	Ope/RFA	NS (P = 0.622)	NS (P = 0.623)
Li <i>et al</i> ^[29]	43 vs 36	LVD with/without ADV	12 mo	Ope	NS (P = 0.077)	Overall survival (P = 0.0094)
Piao <i>et al</i> ^[30]	30 vs 40	LVD	24 mo	Ope/RFA	NS	NS (P = 0.12)
Wu <i>et al</i> ^[31]	518 vs 4051	LVD/ETV/Telbivudine	2.64 yr	Ope	P < 0.001	P < 0.001

HCC: Hepatocellular carcinoma; LVD: Lamivudine; ETV: Entecavir; ADV: Adefovir-dipivoxil; NS: Not significant; NA: Not analyzed; Tx: Treatment.

Table 2 Studies on the effects of interferon on hepatitis B virus-related hepatocellular carcinoma after treatment

Authors	Treated vs Untreated	Treatment	Observation time	HCC Tx	Recurrence	Survival
Someya <i>et al</i> ^[38]	11 vs 69	IFN α	16 yr	Ope/RFA	P = 0.013 (High AST group)	NA
Lai <i>et al</i> ^[39]	35 vs 36	IFN α	30 mo	Inoperable	P = 0.001 (Tumor regression)	P = 0.047
Lo <i>et al</i> ^[40]	40 vs 40	IFN α	60 mo	Ope (Stage III / IVA)	P = 0.031	NS (P = 0.311)
Sun <i>et al</i> ^[41]	118 vs 118	IFN α	36.5 mo (median)	Ope	P = 0.048	P = 0.0003
Chen <i>et al</i> ^[42]	106 vs 109	IFN α	63.8 mo (median)	Ope	NS (P = 0.766)	NS (P = 0.826)

HCC: Hepatocellular carcinoma; IFN: Interferon; NS: Not significant; NA: Not analyzed; Tx: Treatment.

reserve^[28]. Wu *et al*^[31] recently reported that NAs were important in preventing recurrences after liver resection (Table 1).

At present, opinion is divided regarding whether administration of NAs after HCC treatment prevents HCC recurrence^[32]. However, NAs may improve prognosis by improving hepatic functional reserve. NAs treatment was able to improve survival post-HCC treatment compared with no NAs therapy^[33]. Recently, ETV therapy was found to be more effective with a rapid reduction in viral load compared with LVD. ETV is safe and well-tolerated during long-term treatment^[34]. Furthermore, ETV has a higher genetic barrier to resistance^[35]. ETV treatment might have potent protective effects against recurrence of HCC.

EFFECTS OF IFN IN PREVENTING RECURRENCE AFTER CURATIVE TREATMENT FOR HCC

Basic research has shown that IFN has antiviral effects, antitumor effects against HCC^[36,37], and inhibits the proliferation of cancer cells. In a retrospective study by Someya *et al*^[38] evaluating IFN therapy in patients after curative treatment for HCC who also had HBV-related cirrhosis, uni- and multivariate analysis showed that IFN prevented recurrences, especially in the group with high aspartate transaminase. In addition, in a randomized controlled trial (RCT) of high-dose IFN in patients with HCC who could not undergo surgery, the IFN-treated group showed a significantly higher rate of $\geq 50\%$ tumor size reduction compared to the control group^[39]

(Table 2).

Furthermore, RCTs have been conducted to investigate the effects of IFN in preventing recurrences in patients after treatment for HCC. Lo *et al*^[40] conducted a RCT in 40 patients with HBV-related HCC after curative hepatic resection. They compared a group treated with IFN- α 2b 10 MU/m², three times weekly, for 12 wk and a non-treated control group. The 1- and 5-year survival rates in the IFN group were 97% and 79%, respectively, compared to 85% and 61% in the control group (P = 0.137). Multivariate analysis showed that IFN therapy may lower the risk of death. In a subgroup analysis, the 5-year survival rate in stage I / II patients did not differ between the IFN and control groups, but with IFN therapy in stage III/IVA patients, early recurrence of HCC was prevented, and the 5-year survival rate improved from 24% to 68% (P = 0.038). Sun *et al*^[41] also compared an IFN group and control group after HCC surgery in a randomized study. IFN therapy was reported to be useful, with significant increases both in median overall survival and median disease-free survival times. However, the results of a recent phase III randomized study of IFN- α 2b after curative resection for HBV- and HCV-related HCC conducted in Taiwan showed no prevention of HBV or HCV recurrence^[42] (Table 2).

Therefore, the effects of IFN therapy after curative treatment of HCC remain unclear. Pegylated (PEG)-IFN has superseded conventional IFN due to a higher response rate and once weekly administration instead of daily or three times a week. Recently, it was reported that high levels of hepatitis B surface antigen (HBsAg) increase HCC development among hepatitis B envelope an-

tigen (HBeAg)-negative patients with a low viral load^[43]. A recent study clearly showed that the rates of HBsAg clearance after PEG-IFN treatment are substantial and durable in HBeAg-negative patients. Rates of HBsAg clearance were shown to increase further during long-term follow-up, with 12% of patients achieving HBsAg clearance at 5 years post-treatment^[44]. Better results are anticipated in the future using PEG-IFN.

CONCLUSION

Patients with high HBV DNA levels at HCC onset show significantly higher HCC recurrence rates compared to patients with low HBV DNA levels. In patients with high HBV DNA levels, the administration of antiviral drugs relatively early during treatment is recommended to prevent HCC recurrences. However, to more accurately evaluate the effects of antiviral therapy in preventing HCC recurrence, large-scale studies in more patients should be conducted.

Persistent viral suppression by antiviral therapy can inhibit carcinogenesis. Treatment with PEG-IFN results in a higher virological therapeutic response compared with conventional IFN. In addition, ETV, which has become a drug of first choice instead of LVD, has a very low resistance mutation rate, thus long-term viral suppression is possible. The long-term therapeutic effects of PEG-IFN and ETV are currently uncertain, but equal or better efficacy than conventional IFN or lamivudine for the prevention of carcinogenesis is expected. Future research should be aimed at clarifying the effects of antiviral therapy in HBV-related HCC.

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