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TOPIC HIGHLIGHT

2015 Advances in Hepatitis B virus

Management of hepatitis B virus infection during treatment for hepatitis B virus-related hepatocellular carcinoma

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Abstract

Although liver resection is considered the most effective treatment for hepatocellular carcinoma (HCC), treatment outcomes are unsatisfactory because of the high rate of HCC recurrence. Since we reported hepatitis B e-antigen positivity and high serum hepatitis B virus (HBV) DNA concentrations are strong risk factors for HCC recurrence after curative resection of HBV-related HCC in the early 2000s, many investigators have demonstrated the effects of viral status on HCC recurrence and post-treatment outcomes. These findings suggest controlling viral status is important to prevent HCC recurrence and improve survival after curative treatment for HBV-related HCC. Antiviral therapy after curative treatment aims to improve prognosis by preventing HCC recurrence and maintaining liver function. Therapy with interferon and nucleos(t)ide analogs may be useful for preventing HCC recurrence and improving overall survival in patients who have undergone curative resection for HBV-related HCC. In addition, reactivation of viral replication can occur after liver resection for HBV-related HCC. Antiviral therapy can be recommended for patients to prevent HBV reactivation. Nevertheless, further studies are required to establish treatment guidelines for patients with HBV-related HCC.

Key words: Chronic hepatitis B; Liver resection; Hepatocellular carcinoma; Antiviral therapy; Nucleos(t)ide analogs

Core tip: Although liver resection is considered the most effective treatment for hepatocellular carcinoma (HCC), treatment outcomes are unsatisfactory because

of the high rate of HCC recurrence. Many investigators have demonstrated the effects of viral status on HCC recurrence and post-treatment outcomes. Therapy with interferon and nucleos(t)ide analogs may be useful for preventing HCC recurrence and improving overall survival in patients who have undergone curative resection for hepatitis B virus (HBV)-related HCC. In addition, reactivation of viral replication can occur after liver resection for HBV-related HCC. Antiviral therapy can be recommended for patients to prevent HBV reactivation.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer mortality[1,2]. Chronic infection with hepatitis B virus (HBV) is a major risk factor for HCC development. Risk factors for HCC among HBV carriers include male sex and advanced age, longer infection, alcohol consumption, and hepatic fibrosis[3]. The incidence of HCC is reportedly 0.2 per 100 person-years among inactive carriers, between 0.8 and 1.0 among people with chronic hepatitis B infections without cirrhosis, and between 3.2 and 4.3 among patients with compensated cirrhosis[4]. Although liver resection and radiofrequency ablation therapy are curative treatments for HCC, treatment outcomes are often unsatisfactory because of the high rate of HCC recurrence, which includes metastases from primary carcinomas and multicentric carcinogenesis after treatment (*i.e.*, multicentric recurrence). Risk factors for HCC recurrence include tumor factors such as tumor number and vascular invasion, which are related to metastasis from the primary carcinoma. Multicentric carcinogenesis is closely associated with persistent active hepatitis and hepatic fibrosis. Therefore, strategies for both HCC and chronic hepatitis B infection are required to improve the post-treatment outcome of HCC in patients with chronic hepatitis B infections[5]. Liver transplantation is the most radical treatment for HCC as well as the treatment of underlying disease including chronic hepatitis B infection. However, donor shortage is a major problem associated with liver transplantation.

Since we reported in the early 2000s that hepatitis B e-antigen (HBeAg) positivity and high serum concentrations of HBV DNA are strong risk factors for HCC recurrence after curative resection of HBV-related HCC[6-8], many investigators have reported the effects of viral status in HBV-infected individuals on HCC recurrence and post-treatment outcomes[9-13]. These studies suggest controlling viral status is important to prevent HCC recurrence and improve survival after curative treatment for HBV-related HCC. Since we first reported the reactivation of viral replication occurred after liver resection in patients with HBV-related HCC in 2001[14], some investigators have reported the same findings. It is important to prevent such reactivation after liver resection[15-17].

Two types of drugs, conventional interferon (IFN)-α or pegylated IFN (PEG-IFN)-alpha, and nucleos(t)ide analogs (NAs), have recently become available for the treatment of chronic hepatitis B infection. Studies have shown that IFN therapy reduces progression to cirrhosis and HCC development[18,19]. Meanwhile antiviral therapy with NAs including lamivudine (LAM), adefovir dipivoxil (ADV), and entecavir (ETV), suppresses viral replication and appears to be useful for preventing progression to cirrhosis and HCC development in patients with chronic hepatitis B infection[20-26].

This paper reviews the impacts of perioperative antiviral therapy on viral replication reactivation after treatment as well as on HCC recurrence and survival following curative treatment for HBV-related HCC.

REACTIVATION OF HBV REPLICATION AFTER LIVER RESECTION

Reactivation of HBV replication in patients who receive cytotoxic or immunosuppressive therapy is well recognized. Since we first reported the reactivation of viral replication occurring after liver resection in patients with HBV-related HCC[14], some investigators have also reported reactivation after chemoembolization, radiofrequency ablation therapy, and liver resection[15-17]. Reactivation occurred in 20%-30% of patients who underwent liver resection. The risk factors for HBV reactivation include high alanine aminotransferase activity, high viral load, the presence of wild-type DNA, and the detection of hepatitis B core antigen in hepatocytes, which are all features of the immune clearance phase in the natural course of HBV infection[14]. Huang *et al*[27] recently reported antiviral therapy using telbivudine can significantly decrease the perioperative reactivation of viral replication after liver resection for HBV-related HCC. We also did not have experienced acute exacerbation since the induction of NAs. Changes in serum HBV DNA levels should be monitored during the treatment for HBV-related HCC. Antiviral therapy can be recommended for patients with risk factor(s) for HBV reactivation.

EFFECTS OF ANTIVIRAL THERAPY ON OUTCOME AFTER TREATMENT FOR HCC

IFN has been used to treat chronic hepatitis B infection

Table 1 Clinical trials of antiviral therapy after curative treatment for hepatitis B virus-related hepatocellular carcinoma

Author	Year	Study design	Treatment	Adjuvant therapy	Effects of antiviral therapy	
					Tumor-free survival	Overall survival
Interferon						
Sun *et al*[39]	2006	RCT	Resection	Inteferon-α	Postponed	Improved
Lo *et al*[37]	2007	RCT	Resection	Inteferon-α2b	Not significant	Improved in stage Ⅲ/Ⅳ A patients
Chen *et al*[42]	2012	RCT	Resection	Inteferon-α2b	Not significant	Not significant
Nucleos(t)ide analogues						
Kubo *et al*[45]	2007	Prospective cohort	Resection	LAM (with ADV rescue)	Improved	ND
Kuzuya *et al*[48]	2007	Retrospective cohort	Resection or RFA	LAM (with ADV rescue)	Not significant	Improved (tendency)
Yoshida *et al*[49]	2008	Retrospective cohort	RFA	LAM (with ADV rescue)	Not significant	Not significant
Chuma *et al*[11]	2009	Retrospective cohort	Resection or RFA	LAM (with ADV rescue) or ETV	Improved	ND
Koda *et al*[50]	2009	Cohort	Resection or RFA	LAM (with ADV rescue) or ETV	Not significant	Improved
Li *et al*[51]	2010	Prospective cohort	Resection	LAM (with ADV rescue)	Not significant	Improved
Chan *et al*[52]	2011	Retrospective cohort	Resection	LAM or ETV	Improved	Improved
Urata *et al*[44]	2012	Retrospective cohort	Resection	LAM (with ADV rescue) or ETV	Improved	Improved
Wu *et al*[53]	2012	Cohort	Resection	LAM, ETV, telbivudine	Improved	Improved
Su *et al*[54]	2013	Retrospective cohort	Rection	LAM or ETV or Pegylated interferon	Improved	Improved
Ke *et al*[55]	2013	Retrospective cohort	Resection	LAM	Not significant	Improved
Yin *et al*[56]	2013	Cohort including RCT	Resection	LAM (with ADV or ETV rescue)	Improved	Improved
Nishikawa *et al*[57]	2014	Retrospective cohort	Resection or RFA or PEI	LAM (with ADV rescue) or ETV	Not significant	Improved

RCT: Randomised clinical trial; RFA: Radiofrequency ablation therapy; PEI: Percutaneous ethanol injection; LAM: Lamivudine; ADV: Adefovir dipivoxil; ETV: Entecavir; ND: Not determined.

for many years. IFNs are cytokines that possess a variety of biologic properties, including antiviral, immunomodulatory, antiproliferative, antiangiogenic, and tumoricidal effects[28]. Meta-analyses of controlled trials of IFN therapy in HBeAg-positive patients show that patients treated with IFN achieve greater HBeAg losses, suppression of HBV DNA levels, and alanine aminotransferase normalization than untreated control patients[29]. In addition, IFN therapy induces higher rates of hepatitis B surface antigen (HBsAg) seroclearance, resulting in lower rates of cirrhosis development, reduced HCC incidence, and better overall survival[30]. IFN conjugated with polyethylene glycol, *i.e.*, PEG-IFN, has recently become widely used because it is convenient and patients with chronic hepatitis B infections treated with it exhibit clinical outcomes superior to those of patients treated with unconjugated IFN[31]. Several studies show that IFN effectively suppresses HBV replication, reduces HCC incidence, and improves outcomes in patients with chronic hepatitis B infections[32-34]. Although the potential effectiveness of IFN-α as an adjuvant therapy for preventing HCC recurrence has been demonstrated in clinical trials and meta-analyses[35-41], other studies report conflicting results[42,43] (Table 1). Furthermore, while the use of adjuvant IFN therapy in HCC has been studied extensively, it has not yet been accepted as a standard treatment after curative therapy, because previous studies have only involved small numbers of patients and varying types and doses of IFN. Therefore, further studies are required to establish appropriate postoperative therapy with IFN in HCC patients.

We reported that a high serum concentration of HBV DNA is a strong risk factor for HCC recurrence and poor survival after curative HCC resection[44] (Figure 1). Furthermore, we reported that the incidence of HCC recurrence was significantly higher in patients who experienced acute postoperative exacerbations of their hepatitis, showed constantly high serum concentrations of HBV DNA, and showed sustained HBsAg expression postoperatively[45]. Several subsequent studies also demonstrated high serum concentrations of HBV DNA are significantly associated with shorter survival times, with the cause of death being HCC recurrence[6,7,9-13,45]. It is well established that a high serum concentration of HBV-DNA is strongly associated with HCC development[46]. The risk of HCC in such patients is more than 10 times higher than that in patients with low serum concentrations of HBV DNA. Antiviral therapy with NAs including LAM, ADV, and ETV, has recently been reported to be useful for preventing progression to cirrhosis and HCC development in patients with chronic hepatitis B infections[20-26]. Since we reported that LAM may prevent HCC recurrence after curative resection for HCC[47] (Figure 2), several published reports describe the effects of NAs after HCC treatment[11,44,48-57] (Table 1). A recent meta-analysis shows that antiviral therapy with NAs reduces HCC-related mortality and HCC recurrence

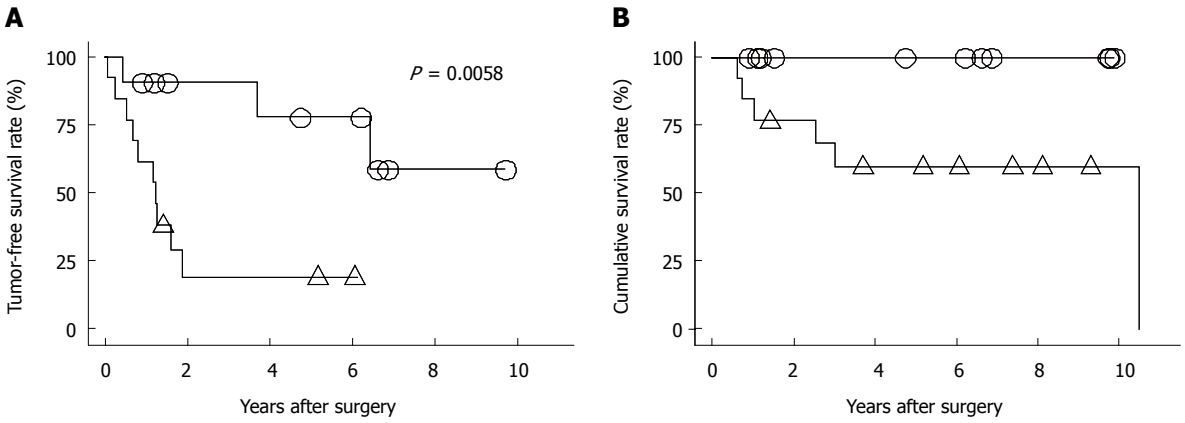

Figure 1 Tumor-free survival (A) and cumulative survival rates (B) after curative resection of hepatocellular carcinoma. Figure adapted from Urata *et al*[44] with permission. Open circles and triangle indicate high and low serum hepatitis B virus DNA concentrations (≥ 4 and < 4 $\log_{10}$ copies/mL), respectively.

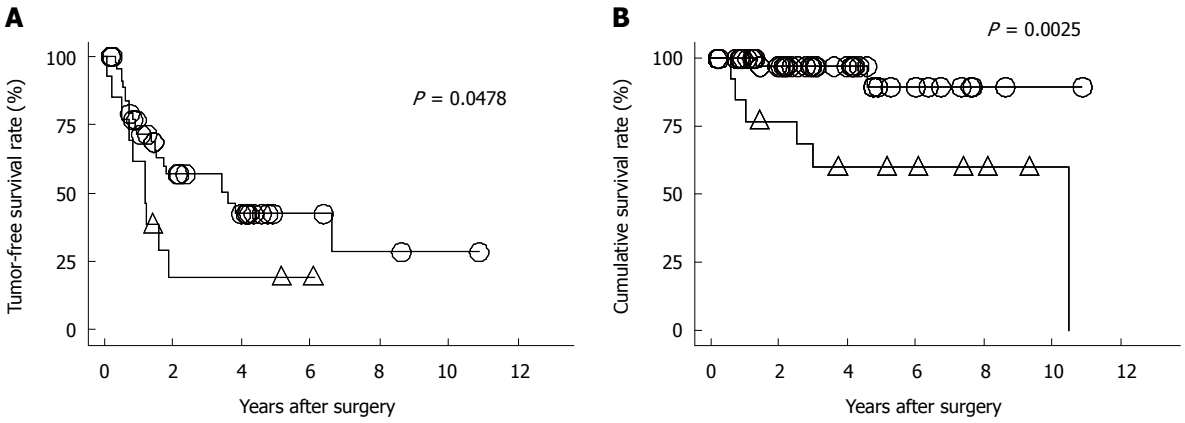

Figure 2 Tumor-free survival (A) and cumulative survival rates (B) after curative resection of hepatocellular carcinoma. Figure adapted from Urata *et al*[44] with permission. Open circles and triangles indicate patients with high serum hepatitis B virus DNA concentrations who were administered and not administered nucleoside analogs, respectively.

postoperatively, and improves overall survival in patients with HBV-related HCC[58-60]. A recent cohort study of patients with chronic hepatitis B infections treated with ETV demonstrates the importance of a sustained virologic response[61]. However, antiviral therapy using NAs cannot suppress HCC recurrence caused by metastases from the original tumor, because NAs do not have any anticancer activity. In addition, NAs cannot prevent multicentric recurrence of HCC, because the HBV DNA will already have been integrated into the host's genome, which is the first step in hepatocarcinogenesis in patients with chronic hepatitis B infections and cirrhosis. Therefore, HCC may still develop despite the effective suppression of viral replication by antiviral agents. A retrospective study of 2795 Japanese patients with chronic hepatitis B infections shows that absence of treatment, male sex, family history of HBV carriage, age over 40 years, fibrosis exceeding grade 2, on a scale of 0-4, and albumin < 40 g/L and platelet count < 150000/mm^3 are independent risk factors for HCC[22]. Close follow-up is necessary for elderly patients who have cirrhosis, even if antiviral therapy has been effective.

We previously showed that antiviral therapy with NAs induces the remission of active hepatitis, maintains liver function, and increases the likelihood of successful treatment for HCC recurrence, even if recurrence developed after curative resection[44]. Similar results were subsequently reported in other studies, namely that antiviral therapy with NAs improved patient outcomes following curative treatment[48,50,51,55,56]. Drug resistance is increasingly emerging in association with long-term antiviral therapy. Hence, the effects of drug resistance on HCC recurrence following treatment for HBV-related HCC must be evaluated.

CONCLUSION

Antiviral therapy after curative treatment aims to improve prognosis by suppressing viral replication. Recent accumulating evidence indicates high serum HBV DNA levels, either preoperatively or postoperatively, is associated with a higher risk of HCC recurrence and that this affects the effectiveness of the antiviral therapy administered after curative treatment for HBV-related HCC. Although IFN has antiproliferative,

antiangiogenic, and tumoricidal effects, IFN therapy may be accompanied by a substantial risk of hepatic decompensation in patients with advanced liver disease. While serum concentrations of HBV DNA become undetectable in most patients who undergo antiviral therapy with NAs, these compounds have no anticancer activity. Therefore, combining IFN and NAs may be an alternative strategy to prevent HCC recurrence after curative treatment for HBV-related HCC. Although IFN therapy and NAs are useful for preventing HCC recurrence and maintaining liver function after treatment for HBV-related HCC, there is insufficient evidence to reach a conclusion and consensus about the optimal perioperative antiviral therapy. Nevertheless, further studies are necessary to establish treatment guidelines for these patients.

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