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Impact of antiviral therapy on post-hepatectomy outcome for hepatitis B-related hepatocellular carcinoma

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Abstract

The outcome after curative resection for hepatocellular carcinoma (HCC) remains unsatisfactory due to the high recurrence rate after surgery. In patients with hepatitis B virus (HBV)-related HCC, which is the majority of patients with HCC in Asia, a high viral load is a strong risk factor for HCC recurrence. It is logical to believe that antiviral therapy may improve the post-operative outcome by promoting viral clearance and hepatocyte regeneration, as well as improving residual liver volume in HCC patients with hepatitis B. However, the effect of antiviral therapy on clinical outcomes after liver resection in patients with HBV-related HCC remains to be established. There are two main groups of antiviral treatment for HBV-oral nucleos(t)ide analogues and interferon. Interferon treatment reduces the overall incidence of HBV-related HCC in sustained re-

sponders. However, side effects may limit its long-term clinical application. Nucleos(t)ide analogues carry fewer side effects and are potent in terms of viral suppression when compared to interferon and are typically implemented for patients with more advanced liver diseases. They may also improve the outcome after curative resection for HBV-related HCC. There are increasing evidence to suggest that antiviral therapy could suppress HBV, decrease the perioperative reactivation of viral replication, reduce liver injury, preserve the liver function before and after operation, and may lower the risk of HCC recurrence. After all, antiviral therapy may improve the survival after liver resection by reducing recurrence and delaying the liver damage by the virus, resulting in a higher chance of receiving aggressive salvage therapy during HCC recurrence.

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Key words: Antiviral therapy; Hepatitis B infection; Hepatocellular carcinoma; Hepatectomy; Liver resection; Outcome

Core tip: The impact of antiviral therapy on clinical outcomes after curative liver resection in patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) remains to be established. There are increasing evidence to suggest that antiviral therapy could suppress HBV replication, decrease the perioperative reactivation of virus, reduce liver injury, preserve the liver function before and after operation, and may lower the risk of HCC recurrence. Antiviral therapy may also improve the survival after liver resection by reducing recurrence and delaying the liver damage by the virus, rendering in a higher chance of receiving aggressive salvage therapy during HCC recurrence. We herein review the currently available evidences on this issue.

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INTRODUCTION

Various therapeutic modalities such as orthotopic liver transplantation (OLT), liver resection, local ablation therapies and transarterial therapies have been used to treat hepatocellular carcinoma (HCC). Traditionally, liver resection and OLT were considered as the main curative treatments for HCC. Due to the shortage of graft, liver resection remains the primary curative treatment in most countries. Recently, there is a dramatic improvement in operative mortality and surgical outcome in liver resection due to the improvement in surgical techniques and advancement in pre-operative assessment. The operative mortality is less than 3%^[1]. The reported 5-year overall survival of HCC after liver resection is 23%-48% in patients with liver cirrhosis and 44%-58% in patients without liver cirrhosis^[2]. Post-resection tumor recurrence and post-resection liver failure remain the main challenges after curative resection^[3,4].

Chronic hepatitis B virus (HBV) infection is the dominant cause of HCC in Asia because of the endemic status of HBV and it inserts major impact on the unsatisfactory post-hepatectomy outcome. Patient with chronic HBV infection is at risk of persistent hepatic inflammation and fibrosis, which may lead to a higher tumor recurrence and a failure to maintain adequate liver reserve at the time of recurrence. On-going hepatic inflammation and cirrhosis favor the process of carcinogenesis, which is related to the duration of exposure and successfulness of immune clearance of hepatitis B. The risk of HCC development is increased in patients with older age and liver cirrhosis^[5].

Even in the absence of cirrhosis, HCC may occur in up to 40% in Asia, in contrary to only 5% in Western countries^[6].

It has been shown that high HBV DNA and ALT levels are associated with tumor recurrence after curative treatment of HCC^[7], which indicates that HBV viral replication has a pivotal role in HCC recurrence. Hepatitis B e antigen (HBeAg) positivity is another risk factor for HCC development^[8,9]. The relative risk was 6 times higher among HBeAg-positive patients than those who were HBeAg-negative. Clearance of HBeAg, whether spontaneous or after antiviral therapy, could reduce the risk of hepatic decompensation, HCC occurrence and improved survival^[10].

Hence, it is reasonable to believe that antiviral therapy may improve the outcome of curative resection in patients with HBV-related HCC by reducing the peri-operative re-activation of hepatitis B and the risk of HCC recurrence after curative treatment.

A Medline search was undertaken to identify articles

that were published from 1990 to 2013 using the keywords “antiviral therapy”, “hepatitis B infection”, “hepatocellular carcinoma”, “hepatectomy”, “liver resection” and “outcome”. Additional papers were identified by a manual search of the references from the key articles.

ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS B

In the last two decades, the development of antiviral therapy was a major breakthrough in the management of chronic hepatitis B (CHB), which modifies the natural history of the disease and reduces the risk of HCC^[11-13]. However, the clinical benefit may be negated by the development of drug resistance^[14]. Currently, nucleos(t)ide analogues with high genetic barrier to resistance, namely entecavir and tenofovir disoproxil fumarate (TDF) are recommended by international guidelines as the first line antiviral treatment for CHB^[15-17]. Antiviral therapy is recommended to all cirrhotic patients with detectable viral load. Its beneficial effect is most obvious in patients with liver cirrhosis^[12,13]. Virological response to entecavir is not affected by the presence of cirrhosis^[18,19]. Interferon treatment reduces cirrhosis, hepatic events and HCC, particularly among responders to treatment^[20,21]; however it is contraindicated in patients with decompensated cirrhosis because it can precipitate hepatic decompensation, resulting in fatal complications^[11,18]. Therefore nucleos(t)ide analogues (NAs) are used exclusively in this subgroup of patients because their side effects are minimal. TDF, emtricitabine/TDF, and entecavir are all well tolerated in patients with decompensated liver disease with comparable improvement in virologic, biochemical, and clinical parameters^[22]. Entecavir-treated patients with decompensated cirrhosis tended to have lower incidence of HCC than those treated with adefovir at 48 wk^[14].

IMPACT OF ANTIVIRAL THERAPY ON PERIOPERATIVE HBV REACTIVATION

How hepatitis B virus infection reacts to liver resection remains an important question to be addressed. Most of the data on HBV reaction towards HCC treatments came from several studies concerning HCC patients received transcatheter arterial chemoembolization (TACE), which involves the administration of chemotherapeutic agents targeted to the liver and raises the concern about HBV reactivation.

Given the curative intent to start with, the clinical course of HBV infection for patients subjected to liver resection may be even more clinically relevant than those receiving TACE. Limited data concerning the risk of HBV reactivation after liver resection are available so far. Although patients undergoing hepatic resections do not receive chemotherapy or immunosuppressive measures that will, theoretically, lead to an increased risk of HBV reactivation, major surgery such as hepatic resections

may significantly modulate or dampen immune responsiveness thereby possibly leading to significant immunosuppression and reactivation of HBV replication during the perioperative period. Furthermore, peri-operative blood transfusion and ischemic injury during hilar clamping may also play a role. Hence, it is logical to believe that hepatectomy can reactivate HBV replication during the perioperative period, especially for patients who do not receive antiviral therapy. It is especially true in patients who did not receive any antiviral therapy^[23,24]. If curative hepatic resection subsequently leads to HBV reactivation, patient outcome may be jeopardized if patients develop fulminant hepatitis^[25].

Thia *et al.*^[26] studied the risk of exacerbation of chronic hepatitis B after liver resection for hepatocellular carcinoma and reported the incidence of all causes of postoperative hepatitis. In this study, 1- and 2-year survival rates were worst for the exacerbation of chronic hepatitis B group at 42.9% and 21.4%, compared with those with postoperative hepatitis due to other causes at 60.3% and 45.2% and those without postoperative hepatitis at 87.7% and 73.5%. All these differences were statistically significant. As a result, the authors recommended routine prophylactic antiviral treatment before partial hepatectomy.

HBV may also be reactivated in the peri-operative period after liver resection for HCC, even among patients with relatively low HBV DNA level (< 200 IU/mL). Huang and colleagues, in a prospective cohort study, found that 10 (6.1%) patients (of whom eight did not receive antiviral therapy prior to operation) among 164 developed HBV reactivation within one month of hepatic resection^[24]. HBV reactivation was more common among those who were not receiving antiviral therapy (21%) compared with those who were (1.6%). More importantly, this study showed that the 3-year disease-free survival rate and overall survival rate after resection in patients with HBV reactivation were significantly lower than those without reactivation. Interestingly, although a low preoperative HBV DNA [< 200 IU/mL (< 1000 copies/mL)] correlated with HBV reactivation on univariate analysis, this correlation was no longer evident after adjusting for the lack of antiviral therapy on multivariate analysis. This phenomenon may be explained in two ways. First, a single HBV DNA level at a given time may not always indicate the permanent immune-suppression of HBV replication, as indicated particularly by the REVEAL analyses data^[27]. Secondly, the apparent correlation between low preoperative HBV DNA level and HBV reactivation was likely secondary to the confounding effect of the use of antiviral therapy, which was not given in a randomized fashion but mainly to those with serum HBV DNA above 2000 IU/mL together with high ALT levels, according to international guidelines. To clarify these, the same group had recently carried out a prospective randomized controlled trial to investigate whether antiviral therapy decreases the risk of perioperative viral reactivation in patients with hepatitis B virus-induced hepatocellular carcinoma. They randomized 84 patients with low viral load to receive

either antiviral treatment with telbivudine or no therapy and found that antiviral therapy with telbivudine could significantly decrease the perioperative reactivation of viral replication in patients with HBV-related hepatocellular carcinoma undergoing liver resection^[28].

There were also studies reported that an effective pre-operative anti-HBV therapy could contribute to an improvement in liver function. The use of nucleos(t)ide analogues such as lamivudine may be useful to reduce the risk of HBV reactivation related to TACE or liver resection^[24,29]. However, more evidence is needed to support indiscriminate use of antiviral therapy to all patients with HBV-related HCC undergoing liver resection.

IMPACT OF ANTIVIRAL THERAPY ON THE RECURRENCE FOR HBV-RELATED HCC AFTER LIVER RESECTION

A number of observational studies have been done to test the impact of HBV DNA and antiviral therapy on HCC recurrence^[30-38]. A study involving 72 patients in Hong Kong demonstrated that high viral load (> 2000 IU/mL) had a significantly higher risk (odds ratio around 20) of HCC recurrence after resection^[31]. However, it should be highlighted that only 10 patients in that cohort received antiviral therapy. Nevertheless, this finding was also supported by a larger Korean study, which showed that persistent HBV viremia was an independent risk factor for increased HCC recurrence after surgery^[31]. On the other hand, one Chinese study and one Japanese study failed to demonstrate the beneficial effect of antiviral therapy in lowering HCC recurrence post-operatively^[33,35]. To clarify the inconsistent findings from these studies, two meta-analyses had been performed^[39,40]. Miao *et al.*^[39] reported that postoperative antiviral therapy in both HBV- and HCV-infected patients has been shown to reduce HCC recurrence up to 5 years. Another meta-analysis focusing on HBV-related HCC by Wong *et al.*^[40] demonstrated that nucleos(t)ide analogues treatment significantly reduced the risk of HCC recurrence after curative treatment by 41%.

The use of antiviral therapy to prevent HCC recurrence has been supported by a recent registry-based study from Taiwan^[41]. When 4051 patients who had never received any antiviral therapy were compared with 518 patients who received oral nucleos(t)ide analogues (lamivudine, entecavir, or telbivudine) for at least 3 mo, the 6-year cumulative incidence of HCC recurrence was significantly lower in the treated cohort (45.6% *vs* 54.6%). Similar to the previous meta-analysis^[40], antiviral agents also offered survival benefits. The 6-year cumulative mortality in the treated cohort was 29.0% compared with 42.4% in the control group^[41]. Table 1 summarized the results of studies on the effect of antiviral treatment in hepatocellular carcinoma recurrence.

Concerning the role as tertiary prevention, despite large sample size and strongly positive results, the study

Table 1 Summary of studies comparing the impact of anti-viral treatment *vs* no treatment in hepatocellular carcinoma recurrence

Ref.	Antiviral	Treated with antiviral		Untreated		OR (95%CI)
		Total	Events	Total	Events	
Wu <i>et al</i> ^[41]	Nucleoside analogue	518	106	4051	1765	0.67 (0.55-0.81)
Li <i>et al</i> ^[33]	Lamivudine	43	33	36	33	0.30 (0.08-1.19)
Koda <i>et al</i> ^[30]	Nucleoside analogue	22	17	14	12	0.57 (0.09-3.42)
Chuma <i>et al</i> ^[34]	Lamivudine, adefovir dipivoxil or entecavir	20	8	64	22	2.57 (1.34-4.94)
Hung <i>et al</i> ^[31]	Lamivudine	10	0	62	30	0.05 (0.00-0.90)
Kuzuya <i>et al</i> ^[35]	Lamivudine	16	7	33	15	0.93 (0.28-3.11)
Kubo <i>et al</i> ^[36]	Lamivudine	14	2	10	5	0.17 (0.02-1.16)
Shuqun <i>et al</i> ^[38]	Lamivudine and thymosin alpha1	16	14	17	17	0.17 (0.01-3.73)
Piao <i>et al</i> ^[37]	Lamivudine	30	14	40	26	0.47 (0.18-1.19)

by Wu *et al*^[41] could not provide a definitive proof for nucleos(t)ide analogues as a treatment for tertiary prevention. It is because a relatively short-term antiviral therapy in months or a few years is unlikely to reverse all the process of cell damage, malignant transformation, and HCC development under the long-term influence of the virus^[42]. Nonetheless, antiviral therapy may enhance post-operative viral clearance, improve residual liver volume, and promote hepatocyte regeneration in HCC patients with active hepatitis B. These effects may significantly improve the tolerance to subsequent therapy and possibly lower rate of recurrence and deaths^[40]. In practice, since nucleos(t)ide analogues are well tolerated and the majority of patients with HCC also have underlying cirrhosis or advanced fibrosis, antiviral therapy is indicated in most patients anyway. Current Asian Pacific guidelines also endorse nucleos(t)ide analogues treatment in all HCC patients with HBV DNA > 2000 IU/mL before and/or after curative therapy of HCC as in HBV patients without HCC^[43].

Interferon treatment as tertiary prevention of HBV-related HCC recurrence remains controversial according to the findings in a meta-analysis and systemic review^[44,45]. Use of interferon treatment in HCC patients may be complicated and even risky, as these patients are more vulnerable to the development of hepatic decompensation with life-threatening complications such as hepatic encephalopathy and ascites^[46]. In contrast, nucleos(t)ide analogues are in general safer and better tolerated than interferon.

IMPACT OF ANTIVIRAL THERAPY ON THE OVERALL SURVIVAL FOR HBV-RELATED HCC AFTER LIVER RESECTION

Theoretically, antiviral treatment may preserve the liver function and render patients with HBV-related HCC able to tolerate HCC treatments better, which should result in a better prognosis and survival. Previous studies have shown that lamivudine and telbivudine therapy could effectively suppress the HBV DNA level and improve the liver function in patients with decompensated cirrhosis^[47-49]. However, evidence on whether antiviral therapy is beneficial to the survival after treatment for HCC is still

limited.

Although there was no significant difference in the survival rate between the two groups, the survival rates in the lamivudine group tended to be higher than those in the control group in a retrospective study of 49 patients by Kuzuya *et al*^[35] ($P = 0.063$). However, this study was limited by a small sample size and a mixture of hepatic resection and radiofrequency ablation as the treatment for HCC. The efficacy of antiviral treatment in HBV patients who underwent curative liver resection for HCC had also been studied by non-randomized and randomized studies^[11,33]. In a recent Chinese study, Li *et al*^[33] compared the impact of antiviral treatment in 79 patients who underwent curative liver resection for HCC. Forty-three patients received lamivudine with or without adefovir as treatment and had a significantly higher HBeAg sero-conversion rate compared with the 36 patients in the control group who received no antiviral treatment. This study showed the efficacy of post-operative antiviral therapy in suppressing viral replication and hence the authors suggested to initiate antiviral treatment in patients with detectable serum HBV DNA level after resection. Liaw *et al*^[11], in a randomized controlled trial, show a significant benefit in the overall survival. They suggested that continuous treatment with lamivudine would lead to a delay in clinical progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis by a significant reduction in the incidence of hepatic decompensation and risk of HCC. However, they did not show a significant effect of lamivudine on HCC recurrence.

Remnant liver function is a major determining factor in selecting subsequent treatment for HCC recurrence and is a key prognostic factor for the overall survival. One interesting finding reported by Li *et al*^[33] was that a significantly greater improvement in the residual liver volume per unit surface area at 6 mo after liver resection in the anti-viral therapy group. Therefore, a higher chance of receiving aggressive salvage therapy during HCC recurrence could be observed among patients receiving antiviral therapy due to better liver reserve, and resulting in a better survival. This finding was further confirmed by the meta-analysis from Wong *et al*^[40].

In Wong's meta-analysis, antiviral therapy has been shown to significantly improve overall survival, as both the mortality related to liver failure and the overall mor-

tality were reduced (by 87% and 73% respectively). The improvement in survival was a result of a lower HCC recurrence as well as improvement in liver function after antiviral therapy^[40].

These results are particularly important because up to now, there is no effective adjuvant treatment to prevent HCC recurrence. There is no proven role for adjuvant chemotherapy or TACE^[50], while the result for molecular targeted chemotherapy is waiting. Anti-viral therapy can be considered as a cost-effective adjuvant therapy for HCC after curative treatment. Nucleos(t)ide analogues, may be preferable than interferon treatment due to less adverse side effects.

CONCLUSION

Tumor factors, cirrhosis and HBV status are predictive of HCC recurrence and survival in patients with chronic hepatitis B. There are increasing evidence to suggest that antiviral therapy could effectively suppress HBV, decrease the perioperative reactivation of viral replication, reduce liver injury, and may lower the risk of HCC recurrence and improve survival after liver resection. In any case, patients on antiviral therapy are more likely to have preserved liver function and tolerate further curative treatment should recurrence occur.

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