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The role of oral antiviral therapy in hepatitis B-related hepatocellular carcinoma

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ABSTRACT

Hepatitis B virus (HBV) is the leading cause of hepatocellular carcinoma (HCC) in places where chronic hepatitis B infection is endemic. Oral nucleos(t)ide analog (NA) therapy can reduce the risk of HCC, but cannot completely prevent its development. For HBV-related HCCs, viral inhibition by NAs can preserve or improve liver function, thereby increasing the chance of therapeutic intervention. After surgical resection, NAs can prevent reactivation of HBV, and also reduce the chance of *de novo* development of HCC in the remnant liver. For those who undergo liver transplantation, NAs are essential to prevent reactivation and graft hepatitis, but is not likely to prevent HCC recurrence, which is due to metastatic disease. The role of NAs for non-curable advanced HCC is less well defined. These include patients undergoing locoregional therapy, chemotherapy, or palliation. Although antiviral therapy can preserve liver function, which may be compromised by HBV, it is unable to prevent disease progression from HCC. At the time of HCC diagnosis, most patients will already be receiving NAs, and these patients should be maintained on therapy. For patients not on antiviral therapy at the time of HCC diagnosis, the decision to commence therapy is often determined by the stage of HCC and life expectancy. Patients undergoing curative therapy, or locoregional therapy/chemotherapy with reasonable life expectancy, should be commenced on antiviral therapy.

INTRODUCTION

An estimated 240 million worldwide are currently infected with the hepatitis B virus (HBV) and have chronic hepatitis B (CHB)[1]. In regions where CHB infection remains endemic, HBV remains the leading cause of hepatocellular carcinoma (HCC)[2]. Although the exact mechanism of hepatocarcinogenesis remains unclear, it is likely that HBV can promote the oncogenic process both directly and indirectly[3]. Direct mechanisms include the integration of HBV DNA into the host genome, leading to genomic instability and malignant transformation[4]. The integration of HBV DNA into genes responsible for cellular proliferation and differentiation may lead to uncontrolled cellular proliferation via altered expressions of oncogenes and tumor suppressor genes. In fact, integrated HBV

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sequences can be observed early in the course of HBV infection, and can be detected in approximately 80% of HBV-related HCCs[5].

Other wildtype/truncated HBV proteins (HBx, HBc, PreS) may also contribute directly towards the development of HCC. HBx is a regulatory protein that acts as a transcription activator by interacting with viral and host regulatory elements. HBx can interfere with the hepatocyte DNA repair system, cell cycle regulation, and apoptosis[6]. Due to the process of DNA integration into the host genome, the HBx gene can be maintained even in the absence of HBV replication[7]. The preS1/preS2/S region encodes a transcriptional activator, which may promote hepatocyte proliferation in the presence of preS mutations. Mutations in the HBV surface proteins can also lead to unfolded proteins accumulating in the cytoplasm and subsequent heightened oxidative stress in the endoplasmic reticulum, contributing to hepatocarcinogenesis[8].

Similar to other chronic liver diseases, HBV can also cause HCC indirectly via chronic necro-inflammation, induced apoptosis, and regenerative activity, with subsequent accumulation of mutations, which may be responsible for malignant transformation. During repeated episodes of chronic inflammation and hepatitic flares, activation and interaction between different cytokines may promote immune escape and alter apoptosis. Inflammation-mediated T cell dysfunction may also impair the immune response against neoplastic cells[9].

From the clinical standpoint, older age, male gender, high viral load, and the presence of cirrhosis are the commonly associated factors for HCC development in CHB patients[10,11]. Of these factors, only viral load can be easily modifiable, and emphasizes the importance of antiviral therapy and its ability to induce complete viral suppression. The REVEAL study demonstrated a linear relationship between serum HBV DNA levels and the risk of developing HCC[10]. This is not surprising, as a high viral load may increase the risk of HCC both directly and indirectly by increasing the chance of oncogenesis with higher rates of HBV integration, and by increasing inflammatory activity respectively. This highlights the importance of viral suppression in preventing HCC development. As hepatitis B e-antigen (HBeAg) is a marker of viral replication, its presence has been associated with the development of HCC[12]. More recently, HBeAg and its precore precursors have been shown to interact with NUMB, leading to reduction of tumor suppressor p53 activity[13]. Other HBV serological markers have also been shown to be associated with HCC development, including hepatitis B core related antigen and hepatitis B surface antigen (HBsAg)[14].

HBV REPLICATION

During the initial stage of infection, the HBV enters the hepatocyte via a host receptor. Once inside the cytoplasm, the relaxed circular DNA (rcDNA) enters the nucleus to form covalently closed circular DNA (cccDNA)[15]. The cccDNA functions as a template for mRNA transcription, which is then transported into the cytoplasm for translation of viral proteins and genomic replication via reverse transcription to form negative-strand DNA. This is followed by formation of positive-strand DNA and rcDNA within the nucleocapsid, which can then undergo further assembly and exported as mature virions, or be recycled back into the nucleus to form cccDNA.

The lack of proofreading mechanism by the HBV polymerase enzyme combined with the high replicative rate leads to high genomic variability with quasi-species containing various mutations. Some of these mutations may be associated with HCC development. These include mutations in the PreS regions as described previously, and drug resistant mutations as result of antiviral therapy. Other mutations associated with higher rate of HCC include the basal core promoter (BCP) mutation (T1762/A1764)[16,17]. The exact mechanism for hepatocarcinogenesis is unclear, although BCP mutations can be associated with disease progression and development of cirrhosis, thereby conferring a higher risk of HCC.

ANTIVIRAL THERAPY FOR CHB

Presently, the only oral antiviral therapy approved for the treatment of CHB infection are nucleos(t)ide analogs (NAs). These are HBV polymerase inhibitors which compete with natural nucleotide substrates that target DNA elongation by acting as chain terminators[18]. NAs may also target other synthetic functions of HBV polymerase, including priming activity, reverse transcription, and the synthesis of DNA[19]. Although interferon-α2b and peginterferon-α2a are approved for CHB infection, it is not used in the setting of cirrhosis or HCC. The currently approved NAs for CHB are lamivudine (LAM), adefovir (ADV), telbivudine, entecavir (ETV), tenofovir disoproxil fumarate (TDF), and most recently, tenofovir alafenamide (TAF). All NAs are formulated as fixed dose tablets to be taken once daily. For patients with HCC, the duration of antiviral therapy is usually life-long. Due to the risk of the development of drug-resistant strains, only compounds

with high potency and high barriers to resistance, such as ETV, TDF, and TAF, should be used[20-22]. A high barrier to resistance ensures that long-term use of these drugs is associated with minimal risk of developing drug resistance. The development of drug resistance leads to virological rebound and subsequent hepatitic flares, leading to higher viral load and increase in inflammatory activity respectively, resulting in higher rates of disease progression[23]. As a result, the risk of developing HCC may be increased. In a meta-analysis of 14 observational studies with 1,284 patients, the one year overall survival and HCC recurrence were significantly reduced and increased respectively with LAM use when compared with ETV[24]. Several studies have also demonstrated a link between the presence of *de novo* drug resistance mutation and the development of HCC, although the mechanism of tumor development remains unclear[25,26].

Long-term oral antiviral therapy has been shown to be effective in preventing and even reversing cirrhosis[27,28]. However, the evidence for preventing HCC is less robust. Although it is likely that antiviral therapy can reduce the incidence of HCC, complete elimination of the risk is not possible[23,29-31]. The paradoxical effect of survival of CHB patients to an older age may increase the risk of development of HCC by allowing time for detrimental effects caused by HBV carriage and HBV DNA integration. The risk is likely highest for those with established cirrhosis, whereby the liver is already at a carcinogenic stage. This may also explain in part why antiviral therapy is unable to fully prevent the development of HCC. To this end, CHB patients are at a lifelong risk of HCC, and should receive appropriate surveillance to enable earlier diagnosis.

For CHB patients who develop HCC, the role of antiviral therapy is even less well defined. Despite this, most patients will receive antiviral therapy, even though the evidence for its use may not be apparent to the prescriber. Given that antiviral therapy is unable to fully prevent HCC occurrence, a proportion of patients will already be on antiviral therapy at the time of tumor diagnosis. For these patients, it is likely that antiviral therapy will be continued irrespective of the therapeutic approach adopted for management of HCC. For patients not on treatment at the time of HCC diagnosis, most will be commenced on antiviral therapy. However this will often be dependent on the stage and treatability of the HCC. Although the clinical scenario may differ depending upon the stage of HCC and the treatment offered, the general indications of antiviral therapy include preserving liver function and prevention of *de novo* or recurrent HCCs.

ANTIVIRAL THERAPY FOR HCC PATIENTS UNDERGOING SURGICAL RESECTION

For patients with preserved liver synthetic function, absence of significant portal hypertension, and resectable tumors, surgical resection remains the best curative option[32]. Compared to HCV, HBV may be associated with less risk of recurrence after resection, although the reason for this is unclear[33]. However, another study has shown a worse prognosis after resection for HBV-related HCCs compared to non-HBV disease[34]. There is evidence to suggest that patients with high viral load at the time of resection are associated with post-resection liver failure and recurrence of HCC[35-37]. Active HBV replication may also be associated with an increased risk of vascular invasion[38]. Given that sufficient remnant liver function is a prerequisite for survival after partial hepatectomy, it would be important to preserve or improve liver function by inhibiting HBV, and to prevent ongoing inflammation or damage which may worsen liver function. For these reasons, all CHB patients with HCC and planning for resection should receive antiviral therapy prior to surgery.

After resection, patients should remain on long-term antiviral therapy. Surgery itself may predispose patients to HBV reactivation after resection, and is a significant cause of hepatitis and liver failure[39,40]. Although the exact mechanism for reactivation is unclear, the stress of partial hepatectomy itself may represent a physiological immunosuppressed state, thereby increasing the risk of reactivation[41]. Factors that may increase this risk include general anesthesia, the use of blood transfusion, and intraoperative ischemic injury. Studies in animal models have also documented that duck HBV (DHBV) reactivation occurs following partial hepatectomy in ducks[42]. It is possible in this case that hepatocytes remaining in the liver after partial hepatectomy will divide to increase the mass of the liver to preoperative levels and these newly divided hepatocytes provide targets for high levels of DHBV infection and replication, which may be detected as postoperative reactivation.

The highest risk for reactivation is likely observed in patients who are not on antiviral therapy[43]. Even for patients with low HBV DNA levels, there is still a risk of postoperative reactivation[44,45]. HBV reactivation may worsen liver function, but has also been associated with recurrence of HCC for those with low viral load at baseline[46].

Recurrence of HCC can occur early (within 2 years) or

late (beyond 2 years) after resection. Early recurrence is usually due to intrahepatic metastasis and is related more to the characteristics of the primary HCC. In contrast, late recurrence is usually as a result of new primary HCC from *de novo* carcinogenesis arising from a premalignant liver. Therefore, the latter is more related to the characteristics of the remnant liver, including the presence of cirrhosis, inflammatory activity, and viral load[47,48]. The fibrotic burden and the presence of cirrhosis may increase the chance of recurrence and reduce disease-free and overall survival after resection[49]. Hence, the use of antiviral therapy after liver resection may also potentially reduce the risk of HCC recurrence. However, this only applies to new primary HCCs, and antiviral therapy is unlikely able to prevent intra- or extra- hepatic disease due to metastasis. To this end, it is likely that antiviral therapy can help to prevent late rather than early HCC recurrences[50,51]. HBV replication and high viral load has been associated with vascular invasion, although this has not been consistently shown[52]. Even for patients with low viral load, those with high levels of HBsAg may be at increased risk of HCC recurrence[53,54].

In fact, the use of antiviral therapy has been shown to be independently associated with reduced risk of HCC recurrence. As expected, the benefits were mainly seen with late rather than early recurrences[55-59]. In a territory-wide study of 2198 CHB patients with HCC from Hong Kong, NAs reduced the risk of HCC recurrence after surgical resection[60]. A meta-analysis of 7,619 postoperative HBV-HCC patients showed more favorable 1-, 3-, and 5-year recurrence-free survival with antiviral therapy compared with no treatment[61]. In another meta-analysis of 12 studies involving 8,204 HBV-related HCC patients, NA therapy significantly reduced the risk of recurrence and improved both disease-free and overall survival[62]. For those with HCC recurrence, a preserved liver function at the time of recurrence via the use of antiviral therapy increased the proportion of patients that can receive curative treatment[63,64]. For patients with repeat hepatectomy for recurrent HCC, antiviral therapy was also associated with better long-term prognosis[65].

ANTIVIRAL THERAPY FOR HCC PATIENTS UNDERGOING LIVER TRANSPLANTATION

For patients who are eligible for liver transplantation, antiviral therapy should be commenced at the time of diagnosis and while they are on the waiting list[66]. The use of antiviral therapy in this setting can prevent acute flares and chronic inflammation, and thus may prevent liver decompensation[67]. The improvement in liver function may also increase the likelihood of patients being able to receive loco-regional bridging therapy. In addition, viral inhibition prior to liver transplantation may reduce the likelihood of recurrence of HBV infection after transplantation. Lifelong antiviral therapy is required after transplantation to prevent graft hepatitis and graft loss. Although liver transplantation is curative for cirrhosis and HCC, it does not eradicate HBV from the host, likely due to the existence of extrahepatic sites of HBV infection. Prior to the availability of effective antiviral prophylaxis, liver transplantation for CHB was a relative contraindication due to the high rate of graft hepatitis and subsequent graft loss. The availability of hepatitis B immune globulin (HBIG) together with LAM was a major milestone in preventing HBV recurrence[68]. HBIG may bind to HBV surface protein to prevent uptake of HBV into the hepatocytes by host receptors, and may neutralize viral particles through the formation of immune complexes[69]. As a form of passive immunoprophylaxis, HBIG has to be administered parenterally at regular intervals to maintain sufficient levels to be effective. Since then, studies have also demonstrated the efficacy of using lower doses, and also replacing HBIG with combination oral antiviral therapy[70,71]. With the introduction of more potent NAs with minimal drug resistance, oral antiviral therapy alone without HBIG has also been shown to be highly effective in preventing graft hepatitis together with excellent long-term outcome[72-75].

The re-appearance of HBsAg and HBV DNA after liver transplantation has been associated with HCC recurrence[76]. Previous studies have shown a temporal relationship between the development of post-transplant HCC recurrence and the re-appearance of HBsAg and HBV DNA[77]. This suggests an association rather than viral factors being a causative factor for recurrence. Despite adequate antiviral therapy in this setting, the reappearance of HBsAg and HBV DNA suggests that the source is possibly tumor in origin, where the antiviral penetrance may be reduced.

ANTIVIRAL THERAPY FOR HCC PATIENTS UNDERGOING LOCOREGIONAL THERAPY

For patients ineligible for surgical resection or transplantation, locoregional therapy (LRT) can be potentially curative, and can offer palliative control for inoperable tumors. The effect of LRT on HBV replication, and the effect of antiviral therapy in this setting are not well defined. Transarterial chemoembolization (TACE) is widely used, and can be effective in reducing tumor progression, with improvement in survival[78]. The delivery of highly concentrated chemotherapy using LRT results in a high

intra-tumor concentration of cytotoxic drugs. Although systemic chemotherapy can be associated with HBV reactivation, it is likely that chemotherapy delivered by TACE poses a far less risk. The lipiodol that is widely used to deliver the drug to the tumor allows for the drug to remain concentrated in the tumor for longer periods, thereby reducing the systemic effect. In addition, the risk of HBV reactivation is dependent on the type of chemotherapeutic agent used. Although doxorubicin can cause HBV reactivation, the risk is likely relatively lower than chemotherapy regimens that contain rituximab and high dose steroid[79].

Several risk factors have been identified for HBV reactivation. These include HBeAg status, viral load, baseline liver function, age, gender, and the intensity of LRT and the use of anthracyclines[80]. However, the data for HBV reactivation following TACE remains somewhat inconclusive, with some studies suggesting increase risk, whereas other studies have demonstrated no changes, or even decline in HBV DNA after chemoembolization[81,82]. The mechanism underlying the decline in viral load remains unclear, and may be due to the natural fluctuation that is independent of the TACE, or possibly from a reduction in tumor load, which may support HBV replication or impair the host immunity. On the other hand, patients with low viral load are still at risk of HBV reactivation after TACE[83]. For patients receiving TACE, prophylactic oral antiviral therapy significantly decreased virological events and hepatitis flares due to reactivation[39,84,85]. Achieving undetectable HBV DNA with antiviral therapy has been shown to significantly improve the progression-free survival in patients receiving TACE[86].

For LRT that does not involve chemotherapy, the data is even sparser. HBV reactivation for CHB patients receiving radiofrequency ablation (RFA) is significantly lower than those undergoing surgical resection, although it still can occur[87]. The pre-RFA viral load has been shown to be associated with HCC recurrence after RFA[88], and the use of antiviral therapy after curative RFA was associated with better outcomes regarding HCC recurrence and overall survival[89]. In a case control study of 399 post-RFA patients, antiviral therapy was shown to be an independent factor associated with a decreased risk of HCC recurrence[90].

Therefore, antiviral therapy should be recommended for those receiving LRT with HBV-related HCC. The likely benefits of antiviral therapy are most likely those that can be observed in the short term. These include improving and preserving liver function, suppressing viral load, prevention of reactivation, and subsequently decrease the risk of hepatic failure after LRT[91]. The longer-term benefits of antiviral therapy are more difficult to assess, given that a significant proportion will succumb to their underling malignancy independent of the HBV status. However, viral suppression may potentially improve long-term survival by reducing HBV reactivation and HCC recurrence[92]. In a systematic review of 994 patients with unresectable HCC receiving LRT, there were significant improvements for progression-free and overall survival in the NA treated group compared with the control group[93].

ANTIVIRAL THERAPY FOR HCC PATIENTS AFTER CHEMOTHERAPY/ IMMUNOTHERAPY

Unlike other solid organ tumors, chemotherapeutic options for HCC remain limited. Sorafenib was approved for the treatment of advanced HCC in 2007. In contrast to the traditional chemotherapy agents, which are associated with immunosuppression, sorafenib may have immunomodulatory function through its effect on T cells, thereby augmenting the immune system[94]. Therefore one would anticipate a low risk for HBV reactivation, although there is currently limited data regarding HBV reactivation with the use of sorafenib. A high baseline viral load has been shown to be an adverse prognostic factor for HBV reactivation and survival in patients with advanced HCC receiving sorafenib[95,96]. In this setting, antiviral therapy may be associated with improve survival, and is a cost-effective approach[95,97,98]. However, in a recent meta-analysis of 3,256 patients receiving sorafenib for advanced HCC, improvement in survival was only observed in HCV patients and not those with HBV[99]. Whether these patients were on antiviral therapy, and its effect on survival, was not studied. In 2017, regorafenib, a multikinase inhibitor, was approved for HCC previously treated by sorafenib. The effect of regorafenib on HBV replication is unknown, although it is likely to be similar to sorafenib. It is likely that the long-term outcome for patients with advanced HCC and receiving palliative chemotherapy/immunotherapy will be unchanged by antiviral therapy, as the survival is limited by the advanced nature of the tumor.

ANTIVIRAL THERAPY FOR PATIENTS WITH UNTREATABLE HCC

For patients with advanced HCC not amenable to treatment, the role of antiviral therapy is limited. Patients will succumb to disease progression arising from the tumor rather than from HBV infection. Therefore, the life expectancy and quality of life is unlikely to be improved with antiviral therapy.

Those already on antiviral therapy should remain on treatment, as there may still be chance of severe flare with cessation of therapy. For those not on antiviral therapies with advanced HCC for palliation, commencing antiviral therapy at this juncture will be futile for the overwhelming majority. Even in the setting of high viral load and elevated transaminases, it may be difficult to confirm that it is due to HBV-related hepatitis rather than locally advanced infiltrative disease. The decision for antiviral therapy in this setting should be made on a case-by-case basis, taking into account the tumor stage and life expectancy of the patient.

SUMMARY

Although direct evidence is sparse, there is a general consensus that antiviral therapy can reduce the risk of HCC in CHB patients. To date, only one randomized placebo-controlled study has been published, showing a reduction in HCC and cirrhosis for advanced CHB patients treated with lamivudine[23]. It is unlikely that future placebo-controlled studies will be performed due to ethical reasons. However, there is increasing circumstantial evidence to suggest that long term antiviral therapy will reduce or delay HCC[100,101]. The key to antiviral therapy therefore is starting early, as the presence of advanced fibrosis and cirrhosis at the time of starting therapy is already associated with higher risk of HCC[102,103].

Once HCC occurs, antiviral therapy is likely still beneficial. The goals of therapy in this instance include HBV DNA inhibition, preservation of liver function, prevention of further disease progression, reduction in the risk of flares, reduction in the risk of HCC recurrence, and hopefully improvement in survival[104]. The choice of antiviral therapy will be dependent on the availability, but in general, a highly potent agent with high barriers to resistance should be used. For HBV-related HCC, ETV has been shown to have better overall survival, decompensation-free survival, and recurrence-free survival compared to LAM[105].

A meta-analysis of 15 studies totaling 8,060 patients with HBV-related HCC after curative therapy showed a better 1-, 3-, and 5-year overall and disease-free survival for those that received NAs[106]. In another meta-analysis of 21 studies including 8,072 similar patients, NA therapy significantly improved recurrence-free and overall survival[58]. Other systematic reviews of HBV-related HCC patients also demonstrated improve survival and reduced early recurrence after curative treatment[107,108]. However, the most important determinant factors for short-term recurrence are likely those related to the tumor. These include the tumor size, number, differentiation, and the presence of lymphovascular permeation. In a large study of 3,855 HBV-related HCC patients, antiviral therapy did not reduce the risk of progressive disease or mortality after adjusting for the tumor status[109].

For those undergoing liver transplantation, recurrence of HCC after transplantation is likely related to pre-transplant tumor factors, rather than from HBV-related factors. Despite this, antiviral therapy is essential for CHB patients to prevent graft loss from reactivation of hepatitis B.

The role of antiviral therapy for those undergoing palliation is less clear, and is likely determined by the stage of HCC and the life expectancy of the patient. It will be prudent to ensure that all HBV-related HCC patients be considered for antiviral therapy, especially with current NAs being extremely safe with minimal side effects and risks. For those with extensive disease and limited life expectancy, where quality of life and survival is determined by HCC rather than HBV infection, the use of NAs is unlikely to be of benefit. For those with less advanced disease and reasonable short-term survival, NAs may preserve underlying liver function and prevent hepatitis flares.

Currently, there are numerous novel agents undergoing development in clinical trials for both HCC and HBV infection. It is likely that NAs will continue to have an important role with viral inhibition. Newer agents will target different sites of the HBV replication cycle, including viral entry, the formation of cccDNA, transcription, viral packaging and assembly, and the release of mature virions[110]. These novel therapies may increase the chance of HBsAg and cccDNA clearance, thereby reducing the production of oncogenic proteins, and potentially reducing the risk of developing HCC.

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Authors' contributions

Concept, literature search, manuscript preparation, manuscript editing, manuscript review: J. Fung
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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

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Not applicable.

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