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Anti-Viral Therapy can Prevent Recurrent Hepatocellular Carcinoma Associated with Hepatitis B: Recent Development

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Abstract

Hepatitis B Virus (HBV) infection is one of the major risk factors for the development of Hepatocellular Carcinoma (HCC) in the world. Anti-viral therapy has helped to reduce the incidence of HBV related HCC and curative treatments are available. Recurrent HCC, however, is a dreaded complication. Recent studies have shown that the hepatitis B viral load is a risk factor for recurrence and anti-viral therapy can therefore reduce the incidence of recurrence and improve overall survival. The aim of this article is to review the recent literature on the effect of anti-viral therapy on prevention of recurrence of HBV related HCC.

Keywords: Hepatitis B virus; Hepatocellular carcinoma; Anti-viral therapy

Introduction

Hepatocellular Carcinoma (HCC) is currently the second most common cause of cancer death worldwide. Most of the burden of disease (85%) is observed in the HBV endemic regions. In the U.S. it is also a known complication of Hepatitis B Virus (HBV) infection among immigrants from the HBV endemic regions. Since the advent of oral anti-viral drugs, namely the Nucleos(t)ide Analogues (NA's), there have been significant advances in the management of HBV related diseases including cirrhosis and HCC. Furthermore, several reports have demonstrated the effects of NA (anti-HBV) therapy in preventing and reversing the cirrhotic process and also in preventing the development of HCC and its recurrence. It appears that anti-viral therapy plays a significant role in preventing HCC recurrence after local treatment such as surgical resection and loco-regional therapy or transplantation. This is especially important as it may impact the burden of liver transplant in the face of desperate shortage of liver grafts. Significantly, in recent years in the United States, a decline of liver transplantation was observed for patients with decompensated liver disease secondary to HBV [1].

The aim of this review is to focus on the effects of anti-viral therapy in preventing HBV-related HCC recurrence.

HBV Related HCC Hepatocarcinogenesis

Those infected with HBV are at risk for HCC. Observational prospective studies have shown that those infected with HBV have an increased relative risk of almost 100 to develop HCC [2]. The viral load is the most important risk factor as shown by Chen et al who found that serum HBV DNA levels greater than 10, 000 copies/mL carried the highest risk for HCC development [3].

Hepatocarcinogenesis associated with HBV infection is not completely understood. Several studies have suggested that the integration of HBV DNA into the host DNA can lead to rearrangement of chromosomes, deregulation and instability of gene expression contributing to oncogenesis [4-6]. The virus itself may also play a direct role via viral proteins such as the HBx protein, a viral regulator gene, which has been implicated to alter host gene expression [7]. Chronic hepatocyte injury with inflammation, cytokine release and fibrosis may also play a role in carcinogenesis.

Incidence and Predictors of HCC Recurrence

Treatment decisions for HCC are guided by tumor staging. If curative options are possible, overall outcomes can be good. However, even after successful interventional therapy, new, recurrent or metastatic tumor can occur and patients die of advanced HCC resulting from uncontrolled HBV infection. Curative therapies for HCC include surgical resection, loco-regional therapies, or liver transplantation. Surgical resection is associated with 5-year survival as high as 70% but also tumor recurrence of 70% at 5 years [8]. Loco-regional therapies include Radiofrequency Ablation (RFA), Trans-Arterial Chemoembolization (TACE) and microwave ablation. Although short-term survival for RFA at 2 years is 98%, tumor recurrence can also be as high as 70% at 5 years [9]. Patients with tumors within Milan criteria who can undergo liver transplantation have the best outcomes with an overall survival of 75% and rate of recurrence free survival of 83% at 4 years [10]. However this maybe an underestimation of recurrence for HBV related HCC as this study included various types of chronic liver disease.

When HCC recurrence occurs, it is important to stratify it as an early or late recurrence. They can be differentiated by the timing and pathogenesis of the recurrence. The cutoff between early and late recurrence is considered 2 years after surgery [11]. Early recurrence is thought to be due to regrowth of micrometastasis that were not detected and would grow in the postoperative period. Late recurrence is considered to be de novo carcinogenesis at different times arising from a new area of dysplastic hepatocytes [12]. Differentiating the type of recurrence is helpful to identify risk factors and has implications on how to prevent recurrence.

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Multiple studies have supported the relationship between HBV viral load and HCC recurrence [13-17]. In a study by Hung et al, 72 patients positive for HBsAg were included and a viral load of greater than 2,000 IU/mL was the most correctable risk factor for HCC recurrence after resection [13]. Kim et al found that those with viremia greater than 10^5 copies/mL was associated with increased recurrence at 5 years, but it had no impact on overall survival [14]. Those treated with loco-regional therapy, such as RFA also has been found to have an association between a viral load greater than 10^4 copies/mL and HCC recurrence [15]. Similarly, in patients who had complete necrosis after TACE, high HBV viral load greater than 10^5 copies/mL was associated with tumor recurrence, early and late [16]. As for patients who underwent liver transplantation for HBV related HCC, those with HBV reinfection were 3.6 times more likely to have HCC recurrence, which supports aggressive long-term anti-viral therapy to prevent HCC recurrence [18].

Prevention of HCC with Anti-Viral Therapy

Given that the carcinogenic process of sustained viremia and continued inflammation contribute to the development of HCC, anti-viral therapy can prevent HCC and its recurrence by controlling HBV viral replication. Anti-viral therapy with NA's is currently the main stay of treatment for chronic hepatitis B. The anti-viral that has been most studied on its effect on HCC is Lamivudine (LAM). Multiple studies have shown that LAM significantly decreases the incidence of HCC compared to placebo [19-22]. The newer anti-viral drugs such as entecavir have also shown to be as effective [23]. It is likely that the same results may be obtained with other NA's.

By the time the first tumor is detected, it is likely that more precancerous foci are in the liver. Without interruption of the carcinogenic process, these lesions may progress to cancer over time. The mechanism by which anti-viral therapy can prevent HCC recurrence is unclear. Perhaps the suppression of viral replication interrupts further integration of HBV DNA into the host DNA. The instability of the DNA maybe then arrested at a certain stage that prevents it from progression to HCC. Also by decreasing the level of viremia, there is less hepatic inflammation and damage. This ultimately leads to less fibrosis, which is often a precursor to HCC. Furthermore, by suppression of the virus (replication), the function of HBx protein may be reduced.

Effect of Anti-viral Therapy on HCC Recurrence and Overall Survival

As anti-viral therapy has been shown to prevent HCC, it appears that it may also have a role in preventing the recurrence of HCC after curative therapy. The data in the literature is overall supportive of anti-viral therapy. Most studies show an improvement in HCC recurrence as well as a benefit in overall survival. A meta-analysis of these studies showed that antiviral therapy reduced the risk of HCC recurrence by 41% [24].

Anti-viral therapy on HCC recurrence after surgical resection

Multiple studies have shown improved HCC recurrence rates with anti-viral therapy after surgical resection. In Japan, Kubo et al in a small retrospective study of patients with high HBV viral load pre and post hepatectomy found that those treated with LAM had improved disease free survival at 5 years [25]. Wu et al, in a larger study of patients after curative resection found that the treated cohort with various anti-virals (LAM, entecavir, or telbivudine) had lower 6-year HCC recurrence rate as well as improved overall survival [26]. Baseline HBV viral load was not provided, but presumed to be high given criteria to start anti-viral in Taiwan in high risk populations. Chan et al in Hong Kong, found that after hepatectomy, those treated with anti-viral therapy (LAM or entecavir) improved disease free and overall survival and more markedly so in those with stage 1 or 2 tumors [27]. These observations suggest that the anti-hepatocarcinogenic effect of anti-viral therapy in recurrence of HCC is due to decreasing HBV viral load (the hepatocarcinogen) and subsequently chronic inflammation. Each of these studies supports the initiation of anti-viral therapy after resection, loco-regional tumor ablation and transplantation.

While most studies have been retrospective studies, a recent randomized controlled trial by Yin et al in China showed that antiviral therapy (LAM, entecavir, adefovir) had improved recurrence free and overall survival after surgical resection. Anti-viral therapy was also effective in improving survival in patients with low viral loads less than 10^4 suggesting all patients with a detectable viral load prior to resection should be started on treatment [28]. Low levels of HBV DNA replication are still associated with expression of HBx protein, a viral protein which strongly promotes oncogenic signaling in hepatocytes [29]. It is likely that anti-viral therapy reduces expression of HBx protein to levels insufficient to promote HCC development.

Anti-viral therapy on HCC recurrence after loco-regional ablation

The effect of anti-viral therapy on HCC recurrence has been less studied in patients after loco-regional therapy. Chuma et al, in Japan, in a study including patients after resection and RFA, found that treated patients with anti-viral therapy had a lower recurrence rate and this difference was more so in those with a high viral load [15]. The first report from the United States was by Hann et al [30]. They compared HCC patients who received anti-viral therapy and those who did not following loco-regional tumor ablation (Figure 1). There was a significant difference in the median survival of 12.5 months versus 60 months for the untreated and the treated (p=0.001). Although numbers were small, it was the longest follow up study with the longest survivors alive over 12 years without recurrence [30].

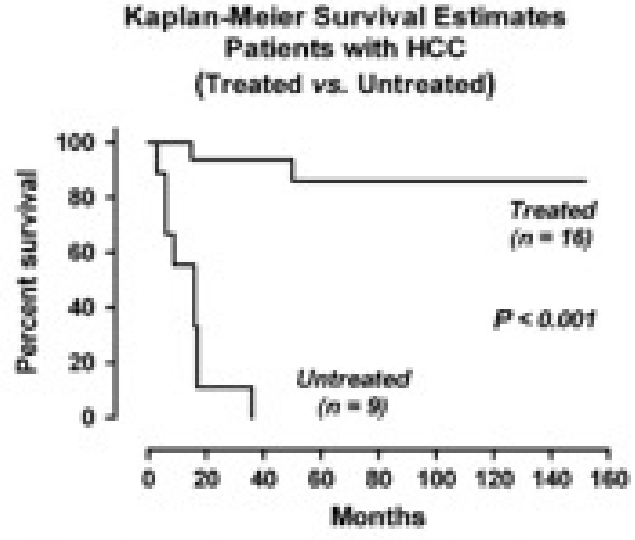

Figure 1: Survival difference between the anti-HBV treated and untreated patients.

Anti-viral therapy and improvement of liver function

Anti-viral therapy not only prevents HCC recurrence as suggested by the studies above, but it improves liver function and subsequently affects overall survival. Li et al found that after resection, there was no difference in the anti-viral treated group compared to the untreated group in early recurrence at 1 year, but had improved overall survival at 1 and 2 years [31]. The treated group had greater residual liver volume and liver function that improved survival and tolerated other treatments for recurrent HCC. The improvement in liver function with anti-viral therapy was also supported by two other retrospective studies [32-33]. The study by Huang et al had similar findings to Li et al with improved overall survival. They did not find improved disease free survival with anti-viral therapy, but did note that an undetectable HBV viral load before post-operative week 24 was associated with late recurrence suggesting the importance of early post-operative viral suppression [34].

Conclusion

Concomitant anti-viral therapy appears to be most effective in preventing recurrence given its impact on the viral load, decrease in hepatic inflammation, and improvement of liver function, leading to improved disease free and overall survival. Some studies suggest that it may even delay or prevent metastasis.

Anti-viral therapy for HCC has several implications. Given its effectiveness after surgical resection and local regional therapy, anti-viral therapy may offer an alternative to liver transplantation and relieve the current graft shortage and more importantly, the concern for de novo malignancy that has been observed in increased frequency among the recipients of liver transplantation [35-37]. It also has an impact on post curative therapy management.

Anti-viral therapy should therefore be started concomitantly regardless of HBV DNA level along with resection or loco-regional tumor ablation. With this approach it is expected to prevent HCC recurrence and improve overall survival.

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