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EDITORIAL

Effect of antiviral treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis B

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Abstract

Chronic hepatitis B (CHB) is a major risk factor for hepatocellular carcinoma (HCC). The prevention of HCC is of paramount importance in patients with CHB, particularly in those with cirrhosis. Antiviral treatment can potentially reduce the risk for HCC since it suppresses viral replication, induces HBeAg seroconversion and improves liver histology. However, most evidence supporting a protective effect of antiviral treatment originates from non-randomized or retrospective studies and is limited to conventional interferon and lamivudine. There is a paucity of data on the effects of pegylated interferon and "newer" oral agents (telbivudine, tenofovir, entecavir) on HCC risk. However, it should be emphasized that the existing randomized control studies in patients with CHB were relatively short-term and not designed to assess the effects of antiviral treatment on HCC risk. Since viral load directly correlates with HCC risk, it is reasonable to hypothesize that the reduction in viral load with antiviral treatment will also lower the risk of HCC. This benefit might become more readily apparent with the newer agents used in the management of CHB which are more effective and have a more favorable resistance profile.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth commonest cancer and the third commonest cause of death due to cancer worldwide[1]. Chronic hepatitis B (CHB) is a major risk factor for HCC[1]. The annual incidence of HCC ranges between 0.3%-1.0% and 2.3%-2.5% in untreated patients with CHB and CHB-related cirrhosis respectively[2,3]. Several potentially curative treatment options exist for patients with HCC including resection, local ablation therapies and liver transplantation[3,4]. In addition, in patients with cirrhosis, surveillance for HCC increases the possibility of an earlier diagnosis and improved survival[5,6]. However, many patients are not candidates for curative treatments because of advanced liver disease and/or advanced HCC; these patients have poor survival rates[3,4]. The shortage of donor organs available for transplantation further limits the potential for liver transplantation[3,4].

PATHOLOGICAL RELATIONSHIP BETWEEN CHB AND HCC

It is apparent that prevention of HCC is of paramount

importance in patients with CHB, particularly in those with cirrhosis. Antiviral treatment has the potential to reduce the risk for HCC since it suppresses viral replication, induces HBeAg seroconversion and improves liver histology[7]. Increased viral load, HBeAg positivity and presence of cirrhosis are all associated with increased risk for HCC[8-10]. More specifically, a direct linear relationship was reported between viral load and HCC risk; patients with persistently high viral load appear to be at particularly high risk for HCC[8,10,11]. Antiviral treatment [particularly interferon (IFN)] can also rarely induce seroconversion from HBsAg to antiHBs[7]. The risk of HCC is significantly reduced in patients who clear HBsAg[12,13]. However, HBV persists at low levels even after HBsAg seroclearance[14,15] and HCC can develop in patients (particularly Asians or patients with cirrhosis) who have cleared HBsAg either spontaneously or after IFN treatment[3,7,14,16,17].

IFN TREATMENT FOR PREVENTING HCC IN CHB

Some studies reported a reduction in the risk of HCC with IFN treatment. In a randomized trial in patients with HBeAg positive CHB, IFN treatment (with prednisolone priming in 54% of the patients) reduced the risk of HCC compared with no treatment[18]. In a non-randomized trial in patients with HBeAg negative CHB, patients who achieved a sustained response to IFN had a lower risk of HCC than those who did not respond to IFN or relapsed after treatment discontinuation[17]. In patients with CHB-related cirrhosis (36% HBeAg positive), IFN reduced the risk of HCC[19]. However, IFN did not reduce the risk of HCC in other studies in patients with HBeAg positive CHB[20,21], HBeAg negative CHB[22] or CHB-related cirrhosis[23-25]. Sung *et al*[26] performed a meta-analysis of 12 randomized, case-control and cohort studies (n = 2742) and reported that conventional IFN reduces the risk of HCC by 34% compared with control patients [relative risk (RR) 0.66; 95% confidence interval (CI) 0.48-0.89]. The risk reduction was greater in patients with early cirrhosis compared with those without cirrhosis and was independent of HBeAg status[26]. In a more recent meta-analysis (11 studies; n = 2082), conventional IFN reduced the risk of HCC in patients with CHB by 41% compared with no treatment (95% CI: 0.43-0.81)[27]. However, in a recent systematic review that assessed only randomized controlled trials (RCT), IFN did not reduce the risk of HCC[28].

Given the direct relationship between viral load and HCC risk, it would be important to evaluate whether the putative preventive effect of IFN against HCC depends on baseline HBV-DNA levels. Most patients in the above-mentioned studies had detectable HBV-DNA regardless of serological status (i.e. HBeAg positive or negative)[17-28]. However, it was not assessed whether the HCC risk reduction during IFN treatment was associated with baseline HBV-DNA levels[17,18,20-28]. Only one study in CHB-related cirrhosis (36% HBeAg positive) reported that IFN reduced the risk of HCC only in patients with higher baseline HBV-DNA levels ($\geq$ 10 Meq/mL) and not in those with lower HBV-DNA levels ($<$ 10 Meq/mL)[19].

LAMIVUDINE TREATMENT FOR PREVENTING HCC IN CHB

In a pivotal RCT in patients with CHB-related cirrhosis or advanced fibrosis (58% HBeAg positive), lamivudine (LAM) significantly reduced the risk of HCC compared with placebo (hazard ratio 0.49; 95% CI: 0.25-0.99; P = 0.047)[29]. When HCC cases diagnosed during the first year of treatment were excluded, the risk reduction was marginally non-significant (P = 0.052)[29]. This trial was terminated early (after a median duration of treatment of 32 mo) because of a significant benefit of LAM[29]. The benefit of LAM was reduced in patients developing resistance to LAM but was not completely negated[29]. In a more recent study, LAM reduced the risk of cirrhosis and/or HCC compared with no treatment in patients with HBeAg positive CHB who had not developed cirrhosis[30]. Importantly, patients developing LAM resistance had smaller benefit than those who did not but the former still had reduced risk of cirrhosis and/or HCC compared with controls[30]. However, in HBeAg negative patients with cirrhosis, those who develop virological breakthrough during LAM treatment appear to be at greater risk for developing HCC compared with those with sustained virological response[31,32]. In the meta-analysis by Sung *et al*[26], treatment with LAM (5 studies, n = 2289) reduced the risk of HCC by 78% compared with control patients (RR 0.22; 95% CI: 0.10-0.50). The benefit of LAM was greater in patients with HBeAg positive CHB[26]. Patients who developed resistance to LAM also showed a reduction in the risk of HCC compared with controls[26]. However, LAM did not reduce the risk of HCC in a recent systematic review of RCT[28]. Adefovir also had no effect[28]. Again, most patients in the above mentioned reports were HBV-DNA-positive but no study assessed whether the potential preventive effect of LAM against HCC development differs between patients with detectable and undetectable HBV-DNA levels[26,28-32].

CONCLUSION

It is still unclear whether antiviral treatment reduces the risk of HCC in patients with CHB. Most evidence supporting a protective effect originates from non-randomized or retrospective studies and is limited to conventional IFN and LAM. There is a paucity of data on the effects of pegylated IFN and "newer" oral agents (telbivudine, tenofovir, entecavir) on HCC risk. However, it should be emphasized that the existing RCT in patients with CHB were relatively short-term and not designed to assess the effects of antiviral treatment on HCC risk[28]. Since viral load directly correlates with

HCC risk, it is reasonable to hypothesize that the reduction in viral load with antiviral treatment will also lower the risk of HCC. This benefit might become more readily apparent with the newer agents used in the management of CHB which are more effective and have a more favorable resistance profile.

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