Interferon Therapy and Prevention of Hepatocellular Carcinoma in Hepatitis C

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Received: 17 January 2012 / Accepted: 18 January 2012 / Published online: 22 February 2012
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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and one of the leading causes of death among patients with cirrhosis. Its incidence is expected to continue increasing over the next 20 years and to peak around 2030 [1]. Although hepatitis B remains the most common risk factor worldwide, chronic hepatitis C virus (HCV) infection is the driving force for the increased incidence of HCC in Western countries and Japan [1]. Therefore, strategies aimed at eliminating the virus may provide opportunities for primary and secondary prevention of the development of HCC.

The first evidence of primary prevention of HCC was from a small randomized controlled trial with 90 HCV-infected patients in which interferon (IFN) treatment was associated with a significant reduction in the incidence of HCC [2]. The beneficial effects of IFN therapy were thought to be related to its anti-proliferative, anti-angiogenic, and/or anti-tumor effects [3, 4]. Since that time, several studies have replicated the findings of a reduction in HCC risk among patients treated with IFN, particularly patients who achieved a sustained viral response (SVR). A meta-analysis found that SVR was associated with a 79% (95% CI 0.73–0.84) reduction in the risk of development of HCC by patients with HCV-related cirrhosis [5]. The primary preventive effect of IFN therapy may be even greater among non-cirrhotic HCV patients, given that SVR at

earlier stages of fibrosis can prevent the development of cirrhosis.

Given that the effect of IFN therapy was primarily seen among patients who had SVR, the utility of maintenance pegylated interferon (PEG-IFN) to prevent disease progression and HCC among non-responders was evaluated. Several randomized trials (HALT-C, COPILOT, and EPIC) have since demonstrated that maintenance PEG-IFN fails to prevent HCC in patients with HCV-related cirrhosis among non-responders [6–8].

Patients with HCC who are diagnosed at an early stage can be effectively treated by liver transplantation, surgical resection, or local ablative therapy [9]. Although liver transplantation effectively treats both the HCC and replaces the underlying cirrhotic liver, it is not possible for all patients, given rigorous selection criteria and a shortage of organs. Surgical resection and local ablative therapy are able to achieve high cure rates, but these patients remain at high risk of developing recurrent or de-novo cancers. Recurrence 5 years after resection of primary tumors is reported to be approximately 50% [10]. Early recurrence seems to be primarily driven by metastases and is associated with factors such as microvascular invasion and AFP level. Late recurrence, i.e., that occurring after 2 years, often appears as de-novo lesions and is associated with factors such as hepatitis activity and persistent HCV viremia [11]. Given the widespread implementation of HCC surveillance programs and increasing burden of HCC, a greater proportion of patients is expected to be diagnosed during early stages and be suitable for either resection or local ablation. Given the associated high incidence of recurrent or de-novo tumors, further studies that address prevention of HCC recurrence are crucial.

Several studies, including five randomized controlled trials and subsequent meta-analysis, have demonstrated

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that HCV treatment after resection or ablation (i.e., secondary prevention) can significantly reduce HCC recurrence in patients with HCV cirrhosis [12]. Although most studies used standard IFN monotherapy, one study included patients who received IFN and ribavirin (RBV) combination therapy and one assessed PEG-IFN monotherapy. HCV treatment seems to be fairly well tolerated by these patients, with 35–100% of patients receiving over 80% of the IFN doses, and is associated with SVR ranging from 4 to 69% across studies. For patients with SVR, incidence of HCC recurrence is approximately 35%, significantly lower than the 61% recurrence among non-responders ($p = 0.005$) [12]. Furthermore, receipt of IFN therapy was associated with significantly improved 5-year survival (OR 0.40, 95% CI 0.23–0.70).

The study by Miyatake et al. [21], in this journal explores an interesting but understudied aspect of the role of HCV treatment in the secondary prevention of HCC. Although several studies have highlighted the benefit of HCV treatment for primary prevention of HCC and its role in the secondary prevention of recurrence in patients who have developed HCC, only a few studies had previously studied the effect of HCV treatment on recurrence before the development of HCC. In this study, 124 patients who received standard IFN monotherapy before the development of HCC (17 patients with SVR and 107 without SVR) were compared with 271 patients who had not previously received IFN therapy. Of these 395 patients, 103 were treated with surgical resection and 292 with local ablative therapy. The choice of curative therapy did not significantly differ between IFN-treated patients and IFN-untreated patients ($p = 0.10$), although surgical resection was performed significantly more often for those who achieved SVR than for non-SVR patients ($p = 0.002$). Although incidence of first HCC recurrence was similar among the groups (36, 47, and 48% at 2 years for SVR, non-SVR, and untreated patients, respectively, $p = 0.41$), incidence of second HCC recurrence was significantly lower among patients with SVR than among the non-SVR group and among the patients who had not previously received IFN therapy. Incidence of second HCC recurrence at 2 years was 10% among those with SVR compared with 69% among those without SVR ($p = 0.003$) and 70% in the IFN-untreated group ($p = 0.006$). The authors found that overall survival was also higher for patients with SVR than for non-SVR and untreated patients, with response to previous therapy being the only independent factor associated with survival ($p < 0.001$).

It is interesting to note in this study that initial recurrence was not significantly different between the groups, despite patients' undergoing IFN therapy a median of 7.2 (range 0.8–17.4) years before the development of HCC. The authors postulate that carcinogenic potential in SVR

patients may be gradually attenuated because of eradication of the HCV infection, whereas it may increase in those with non-SVR, because of the persistence of HCV viremia. This is unlikely to explain this lack of difference, given that most patients were treated several years before the initial curative therapy. This lack of difference emphasizes that early recurrence is driven by intra-hepatic metastases and is more strongly associated with tumor factors than viral factors. Similar to the trials after HCC therapy, the benefit of HCV therapy and SVR is primarily limited to late recurrence, which is more likely to be de-novo tumors [11–13].

This study supports the efficacy of IFN therapy before the development of HCC and its effects on tumor recurrence. Previous studies have analyzed how receipt of IFN therapy [14, 15] and biochemical response [16, 17] before HCC development affect post-treatment recurrence, but this is the first to assess the effect of IFN therapy according to viral response. However, there are important shortcomings of this study that must be taken into account. First, this was a retrospective cohort study which leads to specific biases. Second, patients with SVR had significantly lower Child–Pugh scores than non-SVR untreated patients and therefore, may have been at lower baseline risk of late HCC recurrence. Furthermore, information on other factors known to affect late recurrence, including fibrosis severity and grade of liver disease, were not available for all patients and not included in the multivariate analysis. Finally, these patients were treated between 1995 and 2006 and received standard IFN monotherapy instead of currently available therapy, so SVR was only achieved for a minority of patients. Future prospective studies, preferably randomized controlled trials, are necessary to account for these confounders and to assess HCC recurrence with addition of RBV and protease inhibitors to IFN therapy.

Another important aspect of this study is that only 38% of patients who underwent resection and 29% of patients who underwent ablation actually received IFN therapy before HCC development. This study and others indicate that only a minority of patients with chronic HCV infection are being offered antiviral therapy, with many patients being unaware of the diagnosis [18]. If this trend continues, <15% of liver-related morbidity and mortality caused by HCV would be prevented. Introduction of telaprevir and boceprevir now offers the possibility of greater achievement of SVR with shorter duration of treatment for treatment-naïve and for non-responders to previous antiviral treatment [19, 20].

With growing evidence in support of the efficacy of HCV therapy in HCC prevention, including this study by Miyatake, it is becoming increasingly clear that providers must make a strong effort to offer HCV treatment to appropriate candidates, particularly those with cirrhosis or

advanced fibrosis who are at high risk of developing HCC. Increased treatment and introduction of more potent antiviral agents may not only help prevent future HCC cases but also help improve outcomes for patients who develop cirrhosis and HCC.

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