MINI REVIEW

Does interferon therapy prevent hepatocellular carcinoma in patients with chronic viral hepatitis?

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Summary Chronic hepatitis C and B are well-recognized and potentially preventable risk factors for hepatocellular carcinoma (HCC) development. Clinical and epidemiological studies suggest that therapy with interferon-α may reduce the overall risk of HCC development in patients with chronic hepatitis C, who achieve sustained virological response, but even in those who fail to eradicate the infection. In chronic hepatitis B, interferon therapy reduces the risk of HCC development in HBeAg-positive and cirrhotic patients who achieve persistent suppression of viral replication, while in HBeAg-negative patients the beneficial effect of interferon-α is not definitively confirmed. The preventive role of interferon-α after potentially curative treatment for HCC in both chronic hepatitis B and C is uncertain due to methodological flaws of the existing studies and prospective randomized controlled trials with pegylated interferon-α are needed to clarify this issue.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh in women, accounting for 7% of all cancers, and the third cause of cancer-related death, worldwide [1,2]. Nearly 90 to 95% of all HCCs occur in the context of known and preventable risk factors, such as chronic viral hepatitis, alcohol abuse and cirrhosis [3]. Most HCC cases are attributed to chronic infection with hepatitis B virus (HBV) (55%) or hepatitis C virus (HCV) (25–30%) with the cancer risk being directly related to the clinical and histological stage of the liver disease [3–5]. While cirrhotic patients are at the highest risk, in whom HCC is the most frequent complication and the major cause of liver related death in this patient population [6,7].

Prevention is the only practical option for reducing HCC-related mortality. Primary prevention aims to evade the tumor development with health measures which prevent people exposure to known risk factors like hepatitis viruses or alcohol, or attenuating liver disease progression to HCC. While secondary prevention aims to diagnose HCC at an early, potentially curable stage, tertiary prevention aims to reduce the risk recurrence of the tumor after surgical or percutaneous ablation treatments. Surveillance programs aimed to early diagnose HCC have been widely implemented
in most developed countries, whereas, due to the economic constraints, they are not in place in most developing areas where primary prevention is the only hope for reducing HCC-related mortality [8,9].

The present review will discuss the effect of Interferon-α (IFN-α) treatment on primary and tertiary prevention of HCC in patients with chronic HBV and HCV infection. Indeed, pegylated IFN (PegIFN-α) in combination with the guanosine analogue Ribavirin (Rbv) is the current standard of care of patients with chronic hepatitis C [10], while also being a viable therapeutic option for selected patients with chronic hepatitis B [11,12]. The role of IFN-α therapy in halting hepatitis progression has been recognized, but whether IFN-α therapy prevents HCC development in chronic hepatitis patients, is still debated.

**Does IFN-α have direct anti-neoplastic effects?**

IFN-α is a natural glycoprotein, belonging to type I interferons, produced by the cells of immune system in response to infectious organisms and/or tumor cells. The fact that IFN-α has antiviral, antiproliferative and immunomodulatory actions in various organs and cell lines [13], together with potentially antioncogenic properties, has provided the rationale for its use in the treatment of more than 10 types of cancers for more than 40 years. The anti-tumor effects of IFN-α are complex and still a matter of debate, being likely associated to immunomodulatory and anti-angiogenic responses, as well as to the ability of IFN-α to affect proliferation and cellular differentiation of tumor cells. Both direct and indirect effects of IFN-α result from induction of the so-called IFN-α stimulated genes, which has important pre-apoptotic functions. Indirect immunomodulatory anti-tumor effect of IFN-α includes stimulation of cytotoxic T-cells and natural killer cells, overexpression of the MHC class I expression, which enhances immune recognition, and stimulation of the monocytes differentiation to the highly active dendritic cells, which are the most potent antigen-presenting cells [14,15]. Direct anti-tumor effects involve down-regulation of the oncogene expression, induction of tumor suppressor genes and induction of apoptosis through suppression of anti-apoptotic genes such as Bcl-2 and IAP (inhibitor of apoptosis protein).

In patients with chronic HCV infection IFN-α could suppress liver cell proliferation and stimulate apoptosis of pre-neoplastic liver cells [16]. Accordingly, evaluation of IFNs as therapeutic agents, either alone or as adjuvant in combination with other treatments, focused mainly on tumor and viral diseases.

**HCV-related HCC**

Chronic infection with the hepatitis C virus (HCV) is a major health problem affecting approximately 180 million people worldwide [17]. Although the rate of new cases at the present is declining in most geographic areas, the burden of HCV infection remains substantial due to the high rate of infection before the discovery of the virus in 1989 and the availability of screening tests for anti-HCV antibodies in 1990 [18]. While the prognosis of HCV infection varies accordingly to the rate of fibrosis progression, it has been estimated that the rate of developing cirrhosis development ranges from 5% to 25% over a 25 to 30 year period. Patients with HCV-related cirrhosis develop hepatic decompensation at an annual rate of 30% over a 10 year and a HCC at a rate between 3% and 8%, according to the geographic area [19,20]. Older patients with advanced fibrosis or cirrhosis are at highest risk of HCC [21] and alcohol abuse exerts a synergistic effect with HCV in a dose-related manner: a >60g per day consumption causes approximately a twofold increase in the odds ratio for HCC development [22]. Since HCV eradication is the only intervention that may halt the progression of HCV to cirrhosis, antiviral therapy is also credited to prevent HCV-related HCC, and to improve the quality of life of infected patients [23]. This goal can be achieved by treatment with interferon-based therapies coupled with Rbv, as demonstrated by a number of trials [24–26].

**Primary prevention by IFN-α**

The role of IFN-α in HCC prevention in chronic HCV infection has been a matter of debate since 1995, when a small randomized controlled trial (RCT) demonstrated a decrease in the HCC incidence among the treated patients with HCV-related cirrhosis, compared to untreated controls [27]. The risk ratio of HCC development between treated and untreated patients was 0.67 (95% confidence intervals [CI], 0.009–0.530), indicating that the risk of HCC development was reduced by more than 90% with interferon. This pivotal trial was followed by several retrospective analysis, effectively confirming the aforementioned results, thus suggesting that IFN-α may reduce the incidence of liver cancer in risky population [28–30]. Nevertheless, several factors flaw against the enthusiasm raised by these studies, namely the retrospective design, relatively small sample size and marked population heterogeneity (different stages of disease, duration of follow-up, type of IFN-α and schedule of treatment) and limit their applicability. Additionally, the aforementioned studies were not primarily designed to assess the benefits of IFN-α on HCC prevention, but rather to examine HCC incidence retrospectively, and were not powered enough to catch the hard end-point of HCC, having excluded patients with advanced fibrosis or cirrhosis, who were not eligible for IFN-α therapy, but at high risk for HCC development. In order to shed further light on this relevant issue, in 2001 two meta-analyses examined the effects of recombinant IFN-α in chronic hepatitis C patients in terms of HCC prevention. (Table 1A). Papatheodoridis et al. [31] selected 11 studies reporting HCC incidence after IFN-α treatment in cirrhotic patients, compared to untreated controls. HCC was found to develop more frequently in untreated (21.5%) than in treated patients (8.2%; OR: 3.0, 95% CI: 2.3±3.9, P<0.001). While a sustained response (biochemical in eight studies and both biochemical and virological in three studies) was associated with significant HCC rate reduction (0.9% versus 9%, OR 3.7, 95% CI: 1.7–7.8, P=0.001), a benefit, although less prominent, but still statistically important, was present in non-responders too, compared to untreated patients (0% versus 9%, OR 2.7, 95% CI, 1.9–3.9). Cammà et al. [32] pooling data from 14 studies from cirrhotic and non-cirrhotic patients, concluded that the treatment favoured HCC prevention in cirrhotic...
Table 1: Studies evaluating the effect of interferon treatment on HCC in patients with chronic hepatitis C. A. Meta-analysis.

<table>
<thead>
<tr>
<th>First author, year, ref</th>
<th>Number of studies</th>
<th>Number of patients (treated)</th>
<th>HCC risk in untreated</th>
<th>Versus treated; versus biochemical SR; versus non-SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papatheodoridis G, 2001 [31]</td>
<td>11</td>
<td>2178 (1223)</td>
<td>305</td>
<td>OR 3.0 (95% CI, 2.3—3.9)</td>
</tr>
<tr>
<td>Cammá C, 2001 [32]</td>
<td>14</td>
<td>3109 (1979)</td>
<td>356</td>
<td>11.8% (95% CI 6.4—17.1)</td>
</tr>
<tr>
<td>Alazawi W, 2010 [39]</td>
<td>13</td>
<td>2386 (469)</td>
<td>336</td>
<td>Mean annual percentage rates of HCC 2.52 ± 0.34 for treated and 4.79 ± 0.76 for untreated patients, P=0.02, HR for SVR vs non-SVR 0.46 (95% CI, 0.12—1.76)</td>
</tr>
</tbody>
</table>

CI: confidence interval; HCC: hepatocellular carcinoma; HR: hazard ratio; OR: odds ratio; SVR: sustained virological response

patients with a risk difference −12.8% (95% CI from −8.3 to −17.2, P < 0.00001) with 10 patients needed to treat (NNT) to prevent one HCC. Again, the benefit was most marked in sustained responders (risk difference −19%; 95% CI from −13.1 to −25.2, P < 0.00001) with a NNT of 5. In 2005 the same group updated their meta-analysis with other six studies [33], demonstrating similar results, with a moderate risk reduction (risk difference −12.2%; 95% CI from −8.4 to 16.1, P < 0.00001). Following these meta-analysis it was clear that a sustained virological response (SVR) had a protective effect on HCC development, while it was still unclear if a positive effect of IFN-α in terms of HCC was present also in patients who failed treatment.

This still remained a partially unanswered question even following four prospective observational and three retrospective analysis that examined the role of IFN-α in HCC prevention in the following years (Table 1B). Indeed, while all these studies were significantly better in terms of study design compared to the previous ones, the lack of enrolment of a control arm (untreated patients), for ethical reasons, effectively forced the authors to limit the analysis to the comparison between an SVR and a treatment failure in patients undergoing IFN-based therapies. Yoshida H et al. in the retrospective Inhibition of Hepatocarcinogenesis by Interferon Therapy (IHIT) study that enrolled 2890 patients, 337 (12%) of them cirrhotics, showed that cirrhotic patients achieving an SVR had a reduced risk of HCC development (relative risk (RR) 4.78, 95% CI 1.13—20.18), compared to a RR of 12.23 (95% CI 6.81—21.95) for those not achieving viral eradication (RR 0.516, 95% CI = 0.358—0.742) [34]. The greater benefit in terms of HCC-free survival was seen in cirrhotic males aged 30 to 40 years, who achieved a life expectancy of 48.7 and 39.1 years, with a gain of 16 years, respectively. These results were further confirmed by two prospective trials, one by the same group from Tokyo [35] and another one from Taiwan [36]. In a multicenter retrospective survey including 920 patients with compensated cirrhosis, the incidence rates per 100 persons-years of HCC was 0.66 among patients with SVR and 2.10 among non-SVR (P < 0.001) [37], whereas a failure of achieving SVR was associated with a higher risk of HCC (RR 2.59, 95% CI = 1.13—5.97). In a study in France, conducted by Cardoso et al., including 307 patients with bridging fibrosis or cirrhosis followed for 3.5 years, the incidence rates per 100 person-years of HCC development were significantly lower in SVR, compared to non-SVR patients (1.24 vs 5.85, respectively, HR 34.72, 95% CI = 1.12—8.39, P < 0.001) [38]. Finally, the recent prospective analysis of patients included in the HALT-C trial demonstrated a marked reduction in the HCC incidence among patients with advanced disease who achieve SVR, compared to those who failed to eradicate the infection (HR = 0.19, 95% CI = 0.04—0.80, P = 0.02) [39].

The most recent meta-analysis conducted by Alazawi and colleagues further confirms these results [40]. The analysis of 13 trials including 2386 patients with compensated HCV-related cirrhosis revealed that IFN-based therapy significantly reduces the incidence of HCC, with the mean annual percentage rates being 2.52 ± 0.34 for those receiving IFN-α and 4.79 ± 0.76 for the untreated patients (P = 0.02). However, the aforementioned meta-analysis included both randomized (the minority) and non-randomized (the majority) studies with considerable
Table 1B  Studies, not included in meta-analysis, estimating the effect of IFN-α on HCC prevention in patients with chronic hepatitis C.

<table>
<thead>
<tr>
<th>First author, year, ref.</th>
<th>Study design</th>
<th>Patients (treated)</th>
<th>Treatment regimen</th>
<th>Follow-up (years)</th>
<th>Incidence of HCC (%)</th>
<th>Risk reduction</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiratori Y, 2005 [35]</td>
<td>Prosp.</td>
<td>345(271)</td>
<td>IFNα2a</td>
<td>6.8</td>
<td>17 35 47</td>
<td>Treated vs non-treated HR 0.61</td>
<td>0.41–0.93</td>
<td>0.02</td>
</tr>
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<td></td>
<td>SVR vs no treatment HR 0.31</td>
<td>0.16–0.61</td>
<td>&lt;0.001</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>SVR vs non-SVR HR 0.77</td>
<td>0.51–1.16</td>
<td>0.21</td>
</tr>
<tr>
<td>Hung CH, 2006 [36]</td>
<td>Prosp.</td>
<td>132 (all)</td>
<td>IFNα2b + Rbv</td>
<td>3</td>
<td>4 8</td>
<td>OR 3.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.09–11.36</td>
<td>0.036</td>
</tr>
<tr>
<td>Bruno S, 2007 [37]</td>
<td>Retros.</td>
<td>920 (all)</td>
<td>IFNα2b</td>
<td>12</td>
<td>8 28</td>
<td>HR 2.59&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.13–5.97</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Veldt B, 2007</td>
<td>Retros.</td>
<td>479 (all)</td>
<td>IFNα ± Rbv (261)</td>
<td>2.1</td>
<td>0.6 7</td>
<td>HR 0.46&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.12–1.70</td>
<td>0.25</td>
</tr>
<tr>
<td>Cardoso AC, 2010 [38]</td>
<td>Retros.</td>
<td>307 (all)</td>
<td>IFNα ± Rbv (33)</td>
<td>3.5</td>
<td>6% 14%</td>
<td>HR 4.72&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.12–8.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morgan T, 2010 [39]</td>
<td>Prosp.</td>
<td>1226 (all)</td>
<td>PegIFNα2a + Rbv</td>
<td>7.5</td>
<td>1.1% 8.8%</td>
<td>0.19&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.04–0.80</td>
<td>0.02</td>
</tr>
</tbody>
</table>

BT/R: breakthrough or relapse; CI: confident interval; d: day; HCC: hepatocellular carcinoma; HR: hazard ratio; MU: million units; NR: non-response; OR: odds ratio; PegIFNα: pegylated interferon α; Rbv, ribavirin; SVR: sustained virological response; tiw: trice weekly; w: week; ±: with or without

<sup>a</sup> Non-SVR vs SVR
<sup>b</sup> SVR vs non-SVR
differences in interferon regimens, methods of screening and diagnosis of HCC. This is not a trivial point, as many factors could potentially bias the interpretation of the results, such as the influence of aging, that has long been recognized as an important factor in tumor development. Recently, Ashina et al. [21] demonstrated that >65 years old patients with advanced liver disease are at highest risk of HCC development even after HCV eradication by IFN-α treatment.

Taken altogether, this data supports the concept that an SVR to an IFN-based regimen provides a benefit, in terms of HCC development rates, over to a treatment failure. It should be born in mind however, that the risk of developing a HCC is attenuated, but not completely eliminated by SVR, indicating the need for continuing surveillance for responders with cirrhosis [41]. Although the reasons why some SVR patients experience long-term benefits, while others will still develop HCC during the follow-up are still elusive, it is likely that restoration of the native liver architecture following fibrosis regression might be a key player in this phenomenon. This was suggested by Mallet and colleagues in the retrospective study of 96 HCV cirrhotic patients who underwent a liver biopsy 17 months after the end of antiviral treatment. Cirrhosis regression was observed in 18 (19%) patients (all but one achieved SVR) and associated with significant reduction of clinical events, such as liver decompensation, HCC development and transplantation, in contrast with four SVR patients who did not show cirrhosis regression, while they developed liver complications [42]. Thus, the study shifts the focus from viral eradication to cirrhosis regression as the main determinant of outcome in patients with chronic hepatitis C. Unfortunately, due to the small sample size, the study does not permit the identification of those biochemical or histological variables that we would expect to correlate with a likelihood of cirrhosis regression [43]. If we assume that cirrhosis regression is the histological hallmark of the anti-HCC effect of IFN-based therapies, then we understand why IFN-α failed to prevent HCC in patients with cirrhosis who received maintenance therapy with low-doses of IFN-α. Indeed, the effectiveness of low-dose PegIFN-α maintenance therapy in patients with advanced fibrosis or cirrhosis, not responding to previous treatment of PegIFN-α and Rbv, was evaluated by three RCTs: the HALT-C trial [44], the Epic-3 trial [45] and the COPILOT trial [46]. In all studies no benefit was seen in terms of overall survival, rate of HCC development and hepatic decompensation between treated and untreated patients, despite the improvement of inflammatory markers and the viral load reduction. This notwithstanding that negative results of these multicenter RCTs are counterbalanced by the recently presented data from the HALT-C trial with an extended follow-up period of up to eight years [47], where among patients with cirrhosis at baseline, the cumulative rate of HCC at year 8 was significantly lower in the treated patients compared to controls. The exact figures were 7.8% vs. 24.2%, HR 0.45 (95% CI 0.24—0.83, P = 0.01) for patients with cirrhosis, and 10.1% vs. 9.8%; HR 1.44 (95% CI 0.77—2.69, P = 0.26) for those with advanced fibrosis, demonstrating a modest benefit of long-term PegIFN-α in decreasing the incidence of HCC in patients with established cirrhosis, apparent after more than four years post-treatment, only. This data de facto reinforces the concept that IFN-α may affect HCC development through mechanisms other than viral eradication.

Tertiary prevention with IFN-α

Tertiary prevention of HCC is an important clinical issue as the five-year recurrence rates of HCC are about 75% after curative treatment with hepatic resection or percutaneous ablation of the tumor [48,49]. While tumor recurrence shortly after treatment is more than likely to result from microscopic metastases of the primary tumor, thus requiring effective chemoprevention, later recurrence (after 18 months) commonly represents the onset of a second primary tumor, related to the field cirrhosis risk. While no effective cytotoxic chemotherapy is available to prevent recurrence caused by microscopic metastases, some evidence exists on long-term benefits of adjuvant antiviral therapy in HCC patients who had undergone curative surgery or ablation therapy. According to a recent meta-analysis of 13 trials, all but one study conducted in Asian population, with overall 1180 patients included [50], IFN-α was shown to improve a three-year recurrence-free survival in all but one trial, with an overall risk reduction of 14% (95% CI 8.6—19.4%, P< 0.01). On the other hand, data from three studies, not included in meta-analysis, reported controversial data on preventive effect of IFN-α. In a small RCT from Taiwan, including 20 patients treated with percutaneous tumor ablation and/or transcatheter arterial embolization, antiviral therapy did not delay the first recurrence, whereas the second and the third recurrence rates were significantly reduced in parallel with improved survival [51]. Two other observational studies from Japan failed to demonstrate any benefit of long-term IFN-α treatment after resection or radiofrequency ablation [52,53], but, it should be born in mind that most of these studies were inadequately designed, since they included small number of patients, receiving recombinant IFN-α monotherapy with a low potential for SVR.

Summarizing, the preventive effect of IFN-α on HCC recurrence after potentially curative resection or local ablation needs further evaluation by RCT using currently approved treatment with PegIFN-α in combination with Rbv.

HBV-related HCC

HBV carcinogenesis is a multistage process involving several virus, host and environmental factors. The annual rate of HCC development in patients with HBV-related cirrhosis is 2 to 6% and far less frequently in non-cirrhotic patients [54,55], with a risk being directly linked to older age, male gender, high ALT levels, HBeAg and HBV DNA levels > 2000 IU/mL [11,12,56]. Chronic HBV infection acquired in adulthood has a much lower risk of HCC transformation, than infection resulting from perinatal transmission, probably reflecting differences in the duration of infection [57]. Concurrent infections with HCV, HDV or HIV also increase the risk of cirrhosis and HCC [58], as well as alcohol abuse, cigarette smoking and aflatoxin exposure [58]. A study from China, demonstrated that even modest levels of aflatoxin exposure tripled the risk of HCC in HBV-infected men [59].
Primary prevention

The universal vaccination against HBV of all newborns has generated a formidable barrier to HBV transmission in the youngest. The efficacy of vaccination has already become apparent in several endemic Asian countries, where HCC incidence among children has declined by 70% [60]. Nevertheless, approximately 400 million people remain chronically infected with HBV, who are at increased risk for HCC development. Given that the HCC risk is particularly high in the presence of cirrhosis and/or persistent high viral replication, antiviral therapy is a rational approach to prevent the neoplastic transformation of a HBV-infected liver.

The current therapeutic options for patients with chronic HBV infection include treatment with standard or pegylated IFN-α and oral nucleos(t)ide analogues [11,12]. A recent meta-analysis demonstrated that medium-term treatment with nucleos(t)ide analogue, such as lamivudine monotherapy or lamivudine in combination with adefovir, significantly reduced the risk of HCC, particularly in patients with pre-existing cirrhosis who achieved maintained virological suppression [61]. Conversely, the role of IFN-α in this setting is quite controversial.

Several studies evaluated the effect of recombinant IFN-α on HCC incidence in patients with chronic hepatitis B and further pooled in three independent meta-analyses. The first meta-analysis of seven non-randomized controlled trials in 1505 patients with cirrhosis, suggested a decreased incidence of HCC in IFN-treated patients, as a consequence of three trials conducted in Asia, that gave the pooled estimate in favour of IFN-α versus no treatment of a risk reduction of −4.1% (95% CI −0.8% to 7.0, P < 0.013) [32]. A further meta-analysis demonstrated a moderate risk reduction, which was restricted mainly to patients with cirrhosis, while no decrease in the rate of HCC could be shown in non-cirrhotic patients [62,63] (Table 2). The effect was more prominent in Asian than in European studies, possibly owing to the lower incidence of HCC in Caucasian patients. An important body of evidence supporting the link between viral replication and HCC comes from the studies of HBeAg-positive patients achieving seroconversion to anti-HBe, which is associated with decreased HCC risk [64,65]. Whether IFN-α prevents HCC in HBeAg-positive patients is more controversial, likely owing to lower chances of treatment success, compared to HBe-negative patients [66–68]. However, the aforementioned studies should be cautiously interpreted, since they were primarily designed to assess the antiviral activity of recombinant IFN-α, whether were underpowered to capture such hard points in HBV course, as HCC. Additionally, trials of IFN-α in HBV patients generally trend to enrol subjects with less severe liver disease to increase compliance and treatment tolerability.

While HBsAg seroconversion to anti-HBs is considered the ideal end-point of antiviral treatment, i.e. the clinical surrogate of a cure and is associated with improved survival [69,70], data indicates that the risk of HCC is only attenuated, but not completely eradicated in chronic hepatitis B patients who cleared serum HBsAg, particularly when they are older than 50 years and have advanced fibrosis. These patients, infact, may still

<table>
<thead>
<tr>
<th>First author , year , ref.</th>
<th>Number of patients (treated)</th>
<th>Number of HCC</th>
<th>HCC incidence (%)</th>
<th>IFN-treated (%)</th>
<th>Control (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>Sung J, 2008 [62]</td>
<td>2742 (1292)</td>
<td>190</td>
<td>4.6</td>
<td>9.0</td>
<td>0.66</td>
<td>0.48—0.89</td>
<td>0.006</td>
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<td>0.53</td>
<td>0.36—0.78</td>
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<td>1.1</td>
<td>0.16—3.15</td>
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<td>4.3</td>
<td>0.08—7.23</td>
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<td>IFN-treated (%)</td>
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<td></td>
<td>Control (%)</td>
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<td></td>
<td></td>
<td>RR</td>
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<td></td>
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<td></td>
<td></td>
<td>P</td>
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<td>Overall</td>
<td>12</td>
<td>190</td>
<td>4.6</td>
<td>9.0</td>
<td>0.66</td>
<td>0.48—0.89</td>
<td>0.006</td>
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<td>Cirrhotics</td>
<td>11</td>
<td>110</td>
<td>5.1</td>
<td>8.7</td>
<td>0.61</td>
<td>0.42—0.87</td>
<td>0.004</td>
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<tr>
<td>Non-cirrhotics</td>
<td>11</td>
<td>80</td>
<td>3.8</td>
<td>3.8</td>
<td>1.00</td>
<td>0.33—3.14</td>
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<td>Virological</td>
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<td>80</td>
<td>3.8</td>
<td>3.8</td>
<td>1.00</td>
<td>0.33—3.14</td>
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<tr>
<td>Responders</td>
<td>11</td>
<td>80</td>
<td>3.8</td>
<td>3.8</td>
<td>1.00</td>
<td>0.33—3.14</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Non-responders</td>
<td>11</td>
<td>80</td>
<td>3.8</td>
<td>3.8</td>
<td>1.00</td>
<td>0.33—3.14</td>
<td>0.99</td>
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<tr>
<td>HBeAg-positive</td>
<td>11</td>
<td>80</td>
<td>3.8</td>
<td>3.8</td>
<td>1.00</td>
<td>0.33—3.14</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>11</td>
<td>80</td>
<td>3.8</td>
<td>3.8</td>
<td>1.00</td>
<td>0.33—3.14</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>11</td>
<td>178</td>
<td>5.2</td>
<td>11.7</td>
<td>0.49</td>
<td>0.33—0.83</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  | Meta-analysis evaluating the effect of interferon treatment on HCC in patients with chronic hepatitis B.
Table 3: Interferon treatment and HCC recurrence after curative resection or ablation in patients with chronic hepatitis B.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Patients (treated)</th>
<th>Treatment regimen</th>
<th>Follow-up (years)</th>
<th>Recurrence of HCC (%)</th>
<th>Five-year disease-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun, 2006</td>
<td>236 (118)</td>
<td>IFN-H9251 2bX 18 months</td>
<td>3</td>
<td>57</td>
<td>60 Na Na Na Na 0.04 Na Na</td>
</tr>
<tr>
<td>Someya, 2006</td>
<td>Pilot observ.</td>
<td>IFN-H9251 &gt; 6 months</td>
<td>16.8</td>
<td>27</td>
<td>65 Na Na Na Na 0.06 Na Na</td>
</tr>
<tr>
<td>Lo CM, 2007</td>
<td>RCT TNM I/II</td>
<td>IFN-H9251 2b &gt; 4 months</td>
<td>5.0</td>
<td>35</td>
<td>90 90 90 90 0.07 90 90 90 0.08 Na Na</td>
</tr>
<tr>
<td></td>
<td>TNM III/IV</td>
<td>IFN-H9251 2b &gt; 4 months</td>
<td>70</td>
<td>70</td>
<td>69 69 69 69 0.038 Na Na Na</td>
</tr>
<tr>
<td>Qu, 2010</td>
<td>Retrosp. HCC</td>
<td>IFN-H9251 1b× 18 months</td>
<td>4.4</td>
<td>Na</td>
<td>Na Na Na Na Na 0.082 Na Na Na Na Na</td>
</tr>
</tbody>
</table>

HCC, hepatocellular carcinoma; IFN, interferon; Na, non-available; RCT, randomized controlled trial.

Tertiary prevention

The existing literature on IFN-α therapy after hepatic resection or local ablation of HCC does not support a preventive effect of IFN-α on HCC recurrence [73–76] (Table 3). Many studies, however, were underpowered and rather heterogeneous due to the enrolment of several patients beyond the diagnosis of early cancer, who are at high risk of early tumor recurrence due to early metastases. In HBsAg-negative patients in China an 18 month course of IFN-α was associated with a per protocol reduced five-year mortality with some evidence that the benefits of IFN-α therapy were more a consequence of suppression of hepatitis B rather than the inhibition of tumor recurrence [73]. Two studies, suggesting a benefit of IFN-α on HCC recurrence, had inadequate sample size (< 20 patients) and paradoxically reported the benefit among patients with advanced HCC (stage III/IV), but not among patients with earlier stages of HCC [74]. The most recent retrospective and largest in size study from China in patients with early HCC, demonstrated improved overall survival among IFN-treated patients compared to controls, however showing no differences in five-year HCC-free survival [76].

Summary

Clinical and epidemiological studies suggest that IFN-α therapy may reduce the overall risk of HCC development in patients with chronic hepatitis C, including those with cirrhosis. While sustained responders are the patients who most benefit from treatment, a reduction in HCC incidence is achieved also in non-sustained responders. In chronic hepatitis B, IFN-α therapy reduces the risk of HCC development in HBeAg-positive and cirrhotic patients who achieve persistent suppression of viral replication, while in HBeAg-negative patients the beneficial effect of IFN-α is not definitively confirmed. Up to now, no evidence exists on preventive role of IFN-α after potentially curative treatment for HCC in both chronic HBV and HCV infection. Prospective randomized controlled trials with PegIFN-α are needed to clarify this issue.

Disclosure of interest

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Pietro Lampertico: Advisory Board/Speaker for Bristol-Meyers-Squibb, Roche, Novartis, Gilead, Glaxo Smith Kline.
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References


