Can Therapy of Hepatitis C Affect the Development of Hepatocellular Carcinoma?

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Hepatocellular carcinoma, hepatitis, HCV, chemoprevention, cirrhosis

Abstract
Chronic inflammation induced by viral infections and their role in carcinogenesis is well recognized. Two hepatotropic viruses, hepatitis B and hepatitis C (HCV), have been linked worldwide to the development of hepatocellular carcinoma (HCC). Although orthotopic liver transplant offers the best chance for cure and long-term survival, the demand for organs far outweighs the supply. The incidence of HCC in the United States has increased over the past 3 decades. HCV-induced cirrhosis is believed to play a significant role in the rising rate of HCC. Therefore, primary measures to prevent HCC in HCV-infected patients are urgently needed. Numerous studies of the HCV HCC patient have considered primary treatment with interferon-based therapy. However, secondary prevention currently seems to carry more promise. This article evaluates and assesses various treatments for primary and secondary chemoprevention in the setting of HCV. JNCCN 2006;4:751–757

The interactions between viral infections (and the resulting chronic inflammation) are known to influence the promotion of neoplasia. Two hepatotropic viruses, hepatitis B (HBV) and hepatitis C (HCV), have been associated with the development of hepatocellular carcinoma (HCC). Over the past 3 decades, the incidence of HCC has increased in the United States, mainly attributable to the rise in hepatitis C viral–induced cirrhosis, which has an estimated 2% to 7% annual incidence of HCC. Therapeutic options for HCC are complex because of the presence of an underlying preneoplastic condition, cirrhosis. Ablative liver-directed therapies or resections are often suboptimal treatments because of cumulative local or de novo recurrence rates of 60% to 100% at 5 years. Additionally, the use of such treatments is often limited by the presence of significant hepatic dysfunction caused by underlying cirrhosis.

Orthotopic liver transplant (OLT) offers the best chance for long-term survival after early HCC is detected because it also removes the entire preneoplastic cirrhotic liver. OLT concurrently eliminates the complications associated with portal hypertension. However, because increasing numbers of patients are requiring OLT, prolonged waiting times can often lead to dropout from the transplant list because of tumor progression. United Network for Organ Sharing (UNOS) instituted the Model of End-Stage Liver Disease (MELD) in February 2002 to decrease wait-list mortality. This new allocation system implemented an upgrade for patients with HCC within Milan criteria (a single lesion < 5 cm or 3 lesions < 3 cm, without gross vascular invasion) to expedite access to transplantation for patients with early HCC before tumor progression occurred.

Despite this upgrade, the shortage of organs remains problematic and is expected to worsen as the incidence of HCC escalates. Alarminglly, the number of patients with HCC listed for OLT is predicted to surpass the number of organs available for procurement by 2010. Measures to reduce the incidence of HCC are therefore essential. Elimination of HCV potentially offers a means to prevent HCC. The decline of HBV-induced HCC with the advent of potent antiretroviral therapy underscores the significance of HCC prophylaxis.

Pathogenic Background: Role of Inflammation and HCC

The exact molecular mechanism through which inflammation causes alterations in genetic expression culminating in the development of HCC remains elusive. In HBV, approximately 30% of tumors occur in the absence
Gene expression patterns in HCC have shown promise as a predictive tool of prognosis and may offer insight into therapeutic measures for HCC.\textsuperscript{13} Despite oncogenic properties of some of the viral proteins, the presence of advanced scarring (usually cirrhosis) in HCV is an accepted prerequisite for the development of HCC.\textsuperscript{14,15} Clinical evidence showing that patients with persistently elevated transaminases have an increased risk for HCC compared with those with normal or fluctuating enzyme levels supports the role of inflammation and carcinogenesis in HCV.\textsuperscript{16} This is likely because of ongoing inflammation that ultimately causes cirrhosis. Effective antiviral therapy diminishes inflammation by down-regulating the cell cycle and promoting apoptosis, and is therefore postulated to reduce progression of fibrosis.\textsuperscript{17} Such a chain of events would be expected to reduce HCC rates. Furthermore, sustained virologic response (SVR) to antiviral therapy may also delay or eliminate the need for OLT through hepatic decompensation.

Other superimposed factors can contribute to persistent inflammation in patients with chronic HCV, such as confection with HBV, alcohol use, and nonalcoholic steatohepatitis (NASH).\textsuperscript{18} Modifying these factors is a potential alternative approach to lowering the rate of HCC in patients with HCV.

**Role of Interferon as a Chemopreventative Tool**

Much literature has reported the use of interferon (IFN) and its plausible anticarcinogenic role in chronic HCV. However, the heterogeneity of studies has limited firm conclusions. No standard IFN dose, type, and duration of treatment have been established. Since the use of IFN monotherapy in the early 1990s, significant clinical advances have occurred in HCV therapy, including combination therapy with ribavirin, development of pegylated interferon, and recognition of the therapeutic advantage of weight-based ribavirin.\textsuperscript{19-21} This evolution in therapy has translated into increased SVR rates from approximately 10% with IFN monotherapy to 54% to 56% with combination therapy.\textsuperscript{22,23} Most studies examining the effect of HCV therapy on the development of HCC are limited to IFN monotherapy with historically low SVR rates. Therefore, any significant anticarcinogenic effects of IFN seen in these trials suggest that SVR may not be an absolute prerequisite for overall protection in terms of HCC prevention. IFN stimulates a myriad of genes with potential effects on apoptosis and cell proliferation.\textsuperscript{14}

**Primary Prevention of HCC in Cirrhosis**

**Review of Clinical Studies**

A limited number of randomized controlled trials have studied the effectiveness of IFN in preventing HCC in patients with underlying cirrhosis. Nishiguchi et al.\textsuperscript{25} were the first to report a significant decrease in HCC among 90 patients with HCV cirrhosis randomized to IFN monotherapy for 12 to 24 weeks compared with 45 patients undergoing no therapy. These strikingly positive results are confounded by the very high incidence of HCC in the control group. A single publication included patients treated with combination therapy of IFN plus ribavirin.\textsuperscript{26} No published randomized controlled trials have compared the effects of pegylated IFN plus ribavirin with placebo in the primary prevention of HCC in treatment-naive patients. Such a large-scale randomized controlled trial is unlikely, given the increased efficacy with combination therapy for HCV. Table 1 lists randomized controlled trials that examined IFN and its impact on HCC development in patients with established cirrhosis.

Multiple retrospective studies of the effect of IFN on HCC development have also been published.\textsuperscript{15,20,24} However, inconsistency among methods and lack of randomization makes comparison of reported findings problematic. Three published meta-analyses, including both prospective and retrospective trials,\textsuperscript{29-31} stress the limitations of the included studies, such as the lack of standardized HCV therapy and marked variability in the reported HCC rates among the control groups. Inclusion of retrospective trials introduces the potential for significant differences between the treated and control groups.

Camma et al.\textsuperscript{31} addressed this inconsistency by performing subanalyses based on trial design. These subanalyses considered randomized controlled trial versus nonrandomized controlled trial, presence or absence of imbalance between treated and control groups, ethnicity of patients (European vs. Asian), rate of HCC in the untreated group (at least 20% or < 20%), length of follow-up (at least 60 vs. < 60 months), and publication type (full manuscript vs. abstract). The results were only consistent among pooled data from European randomized controlled trials published as full papers with a follow-up of 60 months or more and an HCC rate of 20% or less in the control group.\textsuperscript{31}

After adjusting for significant confounders, cirrhotic
patients treated with IFN had an odds ratio of 0.28 (P < .0001) for developing HCC. Further analysis using pooled data from consistent results showed that the number of patients needed to treat with IFN to deter the development of HCC was 10, dropping to 5 when only those with SVR were included. Additionally, the authors explored the capability of IFN in preventing HCC in 3798 patients without cirrhosis. IFN treatment showed a small but significant difference (risk difference of 3.6%) in the rate of HCC in those who underwent treatment compared with the controls; however, data were not available to determine how many of these patients had subsequently progressed to cirrhosis. In all 3 meta-analyses, IFN therapy was found to have a positive effect on preventing HCC, although the degree of this effect was small, leading some experts to conclude that definitive evidence supporting the routine use of IFN as a preventive measure for HCC development was lacking.

Shiratori et al. recently published a large-scale, multicenter, prospective trial examining the effect of IFN monotherapy on the incidence of HCC. The cohort consisted of patients with cirrhosis enrolled in 2 separate trials. Of the 345 patients who met inclusion criteria (positive polymerase chain reaction assay for HCV, Child’s A cirrhosis, platelets > 50,000, white blood cell count > 3 * 10^9), 271 underwent IFN therapy and 71 deferred therapy. The treated patients were significantly younger (57 vs. 61) and had higher baseline alanine aminotransferase (ALT) levels (97 vs. 75) compared with the untreated patients. The mean duration of treatment was 39 weeks (26–88 weeks), with 89% of the patients receiving more than 80% of drug for 80% of the treatment period. HCC was diagnosed in 31% of the treated patients and 47.3% of the untreated patients during a median follow-up of 6.8 years (0.04–10.4 years). A significant difference between the 2 groups remained after adjustment for age. Notably, in the original study design, follow-up was 5 years; however, because the number of patients in the treated group who developed HCC was higher than anticipated, follow-up was increased to 7 years. HCC rates were significantly higher in the group that experienced no response (35.3%) compared with those with SVR (17.2%; P < .001). No significant difference in HCC incidence was seen between the patients who experienced no response and those who were untreated. In contrast to prior reports, Shiratori et al. did not find that achieving a biochemical response with normalization of ALT levels in nonresponders had a protective effect. In a multivariate analysis, age, IFN treatment, and albumin levels emerged as independent predictors of HCC.

More impressive were the findings of an overall age-adjusted survival advantage in the treated group compared with the untreated group (hazard ratio = 0.54; P = .02). Only age and IFN treatment were independent predictors of survival. Those experiencing SVR had the greatest survival advantage (hazard ratio = .05 compared with untreated group; P = .03), which became more apparent after 6 years of follow-up. Once patients developed HCC, both groups were treated identically and no difference in survival was seen. Mortality caused by liver failure was higher in the untreated group. Although these findings support an improved survival associated with IFN as shown in

### Table 1 Full Articles of Prospective Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>SVR</th>
<th>HCC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishiguchi et al., 1995</td>
<td>Lymphoblastoid IFN monotherapy 3-6 mo (n = 90) vs. no therapy (n = 45) for 3-6 mo</td>
<td>16% vs. 0%</td>
<td>27% vs. 73%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Valla et al., 1999</td>
<td>IFN monotherapy 48 wk (n = 45) vs. no therapy (n = 39)</td>
<td>Not mentioned</td>
<td>12% vs. 15%</td>
<td>NS</td>
</tr>
<tr>
<td>Bernardinello et al., 1999</td>
<td>Beta IFN 12 mo (n = 38) vs. no treatment (n = 23)</td>
<td>5% vs. 4%</td>
<td>5% vs. 4%</td>
<td>NS</td>
</tr>
<tr>
<td>Azzaroli et al., 2004</td>
<td>Alpha IFN Not treated (n = 30) Treated with IFN + RBV (n = 30)</td>
<td>0% vs. 15%</td>
<td>9 (30%)</td>
<td>–</td>
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<tr>
<td></td>
<td>Previously treated with IFN alone; old “control group” (n = 41)</td>
<td>43% vs. 15%</td>
<td>0 (0%) vs. 15%</td>
<td>&lt;.0003</td>
</tr>
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Abbreviations: NS, not significant; RBV, ribavirin.
other large cohorts, the nonrandomized nature of the study places a caveat on the importance of this finding.

**Alpha-Fetoprotein Levels and HCC**

Alpha-fetoprotein (AFP) has been used as a diagnostic tool for HCC, although its use as a screening tool is limited by its lack of sensitivity and specificity and it should not be used alone to screen for HCC unless imaging modalities are unavailable. In patients with chronic viral hepatitis, the AFP level is often elevated despite the absence of HCC and fluctuates according to the degree of inflammation. Patients with persistently elevated AFP levels have been found to be at higher risk for HCC. IFN therapy has been shown to decrease AFP and ALT levels in patients without HCC, independent of virologic response. This suggests that inflammation itself, rather than the presence of tumor, can elevate AFP levels. The question of whether a decrease in AFP levels associated with IFN therapy predicts a lower risk for developing HCC requires further investigation.

**Maintenance Therapy**

Reports of decreased incidence of HCC with IFN therapy in patients experiencing a biochemical response but no SVR raised the possibility of using long-term IFN therapy to decrease inflammation and potentially lower HCC rates.

A retrospective analysis suggested that long-term IFN therapy was associated with a lower incidence of cancer. Only prospective studies can provide a definitive answer. Three prospective trials (HALT-C, EPIC, and COPilot) in the United States are currently investigating the usefulness of maintenance therapy in patients with advanced fibrosis who experience no response to treatment. One abstract reported results of a study after a follow-up of 2 years that unfortunately showed no impact of IFN on HCC development. However, this study has shown a significant decrease in the development of esophageal varices, suggesting a decrease in portal hypertension with chronic IFN use. Perhaps with longer follow-up, beneficial effects on HCC will become apparent. Further results are awaited; until these results are available, maintenance therapy cannot be recommended for all patients. Those who tolerate therapy well without significant complications and also have advanced fibrosis would be potential candidates for maintenance therapy.

**Secondary Prevention of HCC**

Although data supporting IFN for primary prophylaxis for HCC are less clear, the clinically based evidence supporting the role of IFN treatment for secondary prevention is more convincing. Six randomized clinical trials have shown a lower recurrence rate of HCC among patients who have undergone resection or ablative therapy (transcatheter arterial chemoembolization, percutaneous ethanol injection, radiofrequency ablation, and combinations of these therapies) followed by treatment with varying IFN regimens. The greatest impact of IFN seems to be on the development of distant or later recurrence (> 2 years after treatment) with little to no effect on local, early recurrence (< 2 years after treatment) or first tumor recurrence. These findings imply that early or first recurrences are most likely undetected intrahepatic metastasis present at the initiation of IFN treatment. Those with SVR have shown the greatest benefit in HCC prevention. The length of IFN therapy used in the 6 randomized clinical trials varied widely (from 4 months to 2 years).

An unpublished meta-analysis of the first 5 trials showed a significant reduction effect in HCC recurrence in the patients treated with IFN. However, the effect on overall survival was more ambiguous. Notably, all of these trials have been conducted in Asian populations. The effect of IFN on HCC has not been confirmed in populations with factors known to have a negative impact on SVR, such as race (African Americans) and obesity. Inclusion of such patient populations is needed to determine if the protective effects of IFN can be reproduced.

A recent case-control trial by Hung et al. showed improved survival among 16 patients with Child’s A cirrhosis treated with alfa-IFN plus ribavirin for 24 to 48 weeks, compared with untreated controls who were eligible for therapy but declined. Because these patients had HCV, the SVR rate was higher than would be expected in the presence of cirrhosis, perhaps reflecting that 6 of 10 of those experiencing SVR were non-genotype 1. The analysis also excluded 4 patients with Child’s class B cirrhosis who were unable to tolerate therapy, whose inclusion in an intent-to-treat analysis may have weakened the reported improved survival among the treated group. Nonetheless, these encouraging results merit further analysis in patients treated with pegylated IFN plus ribavirin in whom a higher SVR is anticipated.
Treatment of HCV in Established HCC

Because of potential side effects, treatment for HCV has historically been withheld until HCC has been definitively treated. The ineffectiveness of IFN in decreasing the first or early HCC recurrence after resection/ablative therapy suggests that IFN itself would not have a significant anticarcinogenic effect on an established HCC; however, HCV treatment should be considered in those listed for OLT. It is well established that HCV has a 100% recurrence rate if the patient is viremic at surgery, causing approximately 20% to 30% of patients to develop cirrhosis within 5 years after transplant.55 However, for patients who are virus-free at OLT, approximately 80% of patients will remain negative for HCV replication.56 Treating HCV earlier and achieving undetectable virus before OLT may substantially impact the development of de novo HCC in those who otherwise may develop cirrhosis secondary to recurrent HCV. Further study is needed to validate these data.

The effect of HCV treatment before or after transplantation on HCC recurrence post-transplant is currently unknown. Large randomized clinical trials, such as Low Adult Dose Regimen (LADR), a substudy of the Adult-to-Adult Living Donor Liver Transplant Cohort Study (pretransplant), and the PHOENIX study (posttransplant), are including patients with HCC and may shed some light on this very important question.57

HCC After Viral Eradication with IFN Therapy

Although patients with HCV cirrhosis who experience SVR have an attenuated risk for developing HCC, an appreciable risk for HCC has been reported with long-term follow-up. Ikeda et al.58 retrospectively analyzed 1056 patients who experienced sustained response to IFN monotherapy. After a median follow-up of 4.7 years, 29 patients developed HCC. The cumulative incidence of HCC was 0.5%, 3.3%, 4.9%, and 11% at 3, 5, 7, and 10 years post–IFN therapy, respectively. Multivariate analyses showed that older age, higher AST level, and lower platelet counts before IFN therapy were significantly associated with the development of HCC. The median time from completion of IFN therapy to detection of HCC was 4.6 years (1.4–9 years), illustrating the importance of continued surveillance for HCC despite successful viral eradication. Additional reports of HCC developing more than 5 years after patients experienced SVR showed similar findings, with the highest risk for HCC among older patients with evidence of more advanced fibrosis before initiation of IFN therapy.59 Although the risk for HCC is lower in those with SVR, these findings illustrate that continued screening is warranted, especially in the subset of patients with concomitant risk factors for HCC such as alcohol use, nonalcoholic steatohepatitis, and HBV. Lack of screening for HCC in those with SVR most likely accounts for more advanced HCC (larger tumors and less differentiated) at diagnosis compared with those without SVR.57,58 Nonetheless, a more favorable prognosis has been reported in patients who experienced sustained response after radical therapy compared with those who did not experience response.58,59 This further supports long-term screening in those with advanced fibrosis after SVR.

Non–Viral-Based Chemoprevention

Development of advanced fibrosis secondary to HCV, a known precursor for HCC, occurs over decades and consequently offers substantial time for intervention. Chemopreventative measures have been successful in areas that are endemic with aflatoxin.60 Two agents, oltipraz and chlorophyllin, that have been shown to alter aflatoxin metabolism and biomarkers are available for monitoring. Multiple obstacles exist to identifying a chemopreventative agent in HCV and conducting a randomized controlled trial. Such a study poses logistical problems because of the relatively low incidence of cancer development and the confounding role of morbidity and mortality associated with the underlying liver disease itself. Innovative use of COX-2 inhibitors has shown some promise as a potential agent for chemoprevention, but side effects associated with long-term use in patients with underlying cirrhosis are a concern.61

Conclusions

Increasing numbers of patients with HCV cirrhosis will lead to more patients at risk for HCC. Unfortunately, the OLT will not be able to meet these increased demands. Measures to prevent HCC in patients with HCV are therefore essential. Data on IFN have shown small but positive results in primary prevention; results of prospective trials are eagerly awaited.
awaited. Secondary prevention (i.e., treatment after resection or transplant) is more promising. Researchers hope that the use of more effective approaches, such as combination therapy with pegylated IFN and ribavirin, and anticipated newer medications show a more substantial effect on viral eradication, and hence HCC prevention. Ideally, molecular approaches will enable patients at the highest risk for HCC development to be identified and therapy to be initiated, including chemopreventative measures that can be tailored individually.

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References


Hepatitis C Therapy for Hepatocellular Carcinoma


