Oncology

Oncology 2010;78(suppl 1):17–23
DOI: 10.1159/000315225

Published online: July 8, 2010

Interferon Reduces the Risk of Hepatocellular Carcinoma in Hepatitis C Virus-Related Chronic Hepatitis/Liver Cirrhosis

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Key Words
Hepatitis C · Hepatocellular carcinoma · Interferon therapy

Abstract
The efficacy of interferon therapy against hepatitis C virus (HCV) has much improved, showing a sustained virologic response rate of 40–50% even in the genotype 1b with a high viral load. Several cohort studies conducted in Japan in the 1990s unanimously concluded that the risk of hepatocellular carcinoma (HCC) development was reduced in patients who achieved a sustained virologic response or persistent normalization of alanine aminotransferase as compared to untreated patients. Recently, a large-scale randomized controlled trial, called the HALT-C study, showed no significant difference in the incidence of HCC between patients on maintenance interferon therapy and those without. The reason for the discrepant results in Japanese and USA studies needs further clarification, together with analysis of the difference in incidence rates of HCC among cirrhotic patients. There has also been progress in the treatment of HCC, and together with advances in diagnostics facilitating HCC detection at an early stage, tumor nodules can often be completely removed either by medical ablation or surgical resection. Nevertheless, recurrence of HCC after apparently curative treatment is extraordinarily frequent, since the remaining liver is still at a high risk of HCC. The prevention of the recurrence of HCC, or tertiary prevention, is currently one of the most challenging tasks in hepatology.

Introduction

Recently hepatitis C virus (HCV) infection seems to have spread worldwide, especially in industrialized countries [1]. HCV is transmitted as blood-borne infection with a much weaker infectivity than hepatitis B virus (HBV). The recent rapid spread of HCV infection must be associated with some artificial changes in environment. In Japan, mortality from hepatocellular carcinoma (HCC) has more than tripled since the mid 1970s [2]. The emerging cases of HCC were typically negative for HBV and developed in patients with so-called non-A/non-B hepatitis, which was later revealed to be almost entirely equal to chronic hepatitis C. At present, HCV infection is responsible for about 75% cases of HCC in Japan, whereas HBV is responsible for 10–15% [3]. About 40% of HCV-related HCC patients in Japan have a history of blood transfusion, and typical patients received blood transfusion in the 1950s or 1960s. During that period supply for blood transfusion in Japan was dependent on paid blood

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donors, many of whom were also injecting-drug users, mainly methamphetamine. HCV is thought to have spread first among these subjects in Japan after the end of World War II. The reuse of syringes and needles in medical practice during that period may have contributed to further viral spread. Commercial blood banks were entirely abolished by 1969 in Japan and were succeeded by the Japanese Red Cross Society which collects blood on a totally voluntary basis. Syringe and needle reuse was strongly discouraged in the 1970s. Thus, the spread of HCV in Japan started to decline in the 1970s, although HCV transmission through blood transfusion continued until the advent of a sensitive HCV detection system in the early 1990s.

There was an interval of at least 30 years between the peak of HCV viral spread among the general population and the peak incidence of HCV-related HCC in Japan. Considering the interval of 20 years between the viral spread peaks in Japan and the USA, and also the fact that it takes 20 years or longer from the onset of HCV infection to HCC development, a further increase in HCC incidence in the USA is, unfortunately, most probably inevitable [4, 5].

It has been indicated that interferon (INF) is effective against at least some cases of non-A/non-B hepatitis. Shortly after the discovery of HCV, the effectiveness of IFN against HCV infection was confirmed [6, 7]. IFN monotherapy was licensed by the Japanese national health insurance program in 1992, and more than 200,000 patients with chronic hepatitis C were treated with IFN. According to the licensed 6-month protocol of IFN monotherapy, about 30% of the treated patients showed a sustained virologic response. Pretreatment factors predictive for the response were extensively studied, and it was shown that low serum virus load and non-1b HCV genotypes are the strongest factors favorable for the virologic response [8]. Unfortunately, the cases least responsive to IFN therapy, namely, those infected with high-load 1b genotype HCV, constitute the majority of chronic hepatitis C patients in Japan, among whom conventional IFN monotherapy achieved a sustained virologic response in far less than 10% of patients.

Subsequently two major improvements were introduced to IFN-based antiviral therapy against HCV infection. One is the combination of IFN with the oral agent ribavirin. Ribavirin is an antiviral drug first synthesized in 1970 and active against a number of DNA and RNA viruses. Although the drug is not practically effective against HCV when administered alone, combination therapy with IFN and ribavirin showed a sustained virologic response rate exceeding 20% in patients with high-viral-load genotype 1b. The other major improvement is the development of pegylated IFN, also called Peg-IFN. Polyethylene glycol, or Peg, is covalently attached to IFN molecule in Peg-IFN, resulting in a substantial elongation of the serum half-life of the drug. Peg-IFN is administered usually once weekly subcutaneously. This alleviates patients' burden, facilitating long-term treatment. There are currently two licensed products of Peg-IFNs; the 12-kDa Peginterferon alfa-2b (Peg-Intron, Schering-Plough Corporation, Kenilworth, N.J., USA) and the 40-kDa Peginterferon alfa-2a (Pegasys, Hoffmann-La Roche, Nutley, N.J., USA). The combination of Peg-IFN and ribavirin was naturally the next step to be taken, and is currently the standard therapy for chronic hepatitis C, showing a sustained virologic response rate of 40–50% even in genotype 1b with high viral load [9, 10]. In addition to genotype 1b and high viral load, the factors associated with compromised response to the combination therapy include older age, the presence of liver cirrhosis or advanced fibrosis, and obesity. Although the quality of life of patients during treatment may have been improved by the advent of Peg-IFN, adverse side effects intrinsic to IFN, including fatal ones such as interstitial pneumonitis and suicide attempts, may still accompany treatment with Peg-IFN. Ribavirin is teratogenic, and contraception is imperative. In addition, ribavirin often causes hemolytic anemia, which makes treatment in patients with ischemic cardiovascular diseases or chronic renal failure very challenging.

Since HCV infection is the primary etiology of HCC in Japan and several other countries, it should be shown that antiviral therapy is associated with a reduction in the incidence of the cancer. It is not as obvious as it may seem. HCV is an RNA without reverse transcriptase and does not integrate into the host genome. Although the pathogenesis of HCV-related HCC has not been well clarified, there is no indication suggesting a direct involvement of the presence of HCV in hepatocarcinogenesis. Therefore, viral eradication does not necessarily result in a simultaneous reduction in the risk of HCC. An abundant literature has indicated that cirrhosis is the strongest risk factor for HCC development [11, 12]. It seems appropriate to presume that antiviral therapy will finally reduce the incidence of HCC by preventing progression to cirrhosis. However, it was not known whether the risk diminishes immediately once HCV has been controlled, with at least temporarily persisting cirrhosis. Here, we will focus on the relationship between antiviral therapy and the risk of HCC development.

Risk Factors for HCC Development

In chronic hepatitis C, the risk of HCC development increases rapidly with the progression of liver fibrosis [12, 13], and chronic hepatitis C patients with cirrhosis are at a very high risk of HCC. In Japan, as mentioned earlier, HCV infection spread nationally in the 1950s and 1960s and, after a few decades required for progression to cirrhosis, many patients are at an extreme risk of HCC development. In addition to the degree of liver fibrosis, male gender, older age, and heavy alcohol consumption are also known risk factors for HCV-related HCC [12, 13]. Gender and age are static factors that cannot be changed and the values are obvious. Alcohol consumption is a variable factor and the value is known to the patients themselves. On the other hand, the degree of liver fibrosis is usually not known unless properly examined.

Evaluation of the degree of liver fibrosis is of paramount importance in risk assessment of HCC development in patients with chronic liver diseases, especially chronic hepatitis C. Histological evaluation of liver biopsy samples has been considered the gold standard for the assessment of liver fibrosis [14]. However, the invasiveness accompanying liver biopsy poses a considerable problem with its clinical feasibility. In clinical practice, repeated assessment of liver fibrosis will often be required because a once non-cirrhotic liver may change into cirrhosis over time, sometimes rather rapidly. Consequently noninvasive evaluation of liver fibrosis is one of the main themes of current hepatology.

In transient elastography, shear waves are emitted into the liver and their velocity is measured with ultrasound. Since the velocity is directly correlated with elasticity, or liver stiffness, the degree of fibrosis can be noninvasively measured. The close correlation between the degree of histologically assessed liver fibrosis and liver stiffness measured by transient elastography has been well confirmed [15, 16]. The cutoff value for the diagnosis of histological cirrhosis is reported to be 12.5–14.9 kPa. Higher values of liver stiffness in the range of cirrhosis may indicate the need for further attention for HCC development [17].

Prevention of HCC Development

To establish the evidence of HCC prevention by antiviral therapy against HCV, prospective studies are required. Two representative study designs are randomized controlled trial (RCT) and cohort study. The statistical power of detecting a preventing effect of an antiviral therapy on HCC development depends on the number of events, in this case the number of patients who will develop HCC. Thus patients with cirrhosis are a preferable target of such studies, especially RCTs, because we can detect the preventive effect on HCC development with smaller sample size, provided that there is indeed such an effect.

In fact there are only few papers reporting RCTs on the suppression of HCC development with IFN therapy. In 1995, Nishiguchi et al. [18] reported the results of an RCT among hepatitis C patients with compensated cirrhosis. Forty-five patients each were assigned to receive IFN therapy or non-treatment. HCC developed in 2 of 45 patients treated with IFN in 4.4 years of observation, and 17 of 45 patients in the control arm in 5.5 years. The risk ratio of HCC development between treatment and non-treatment was calculated as 0.067 (95% CI 0.009–0.530), indicating that the risk of HCC development was reduced by more than 90% with IFN. The notion of reducing the risk of HCC development at the cirrhotic stage by IFN was met with a certain amount of skepticism. The main concerns were about the high incidence rate of HCC in the non-treatment group and also about the reduction in HCC incidence in the IFN-treated group, despite the low sustained virologic response rate of 15%. As for the former issue, the annual incidence rate of HCC in the non-treatment group was 6.9% and actually not as high as the incidence rate in Japanese cirrhotic patients. As for the latter, Nishiguchi et al. [19] in 2001 reported long-term follow-up data of the subjects, with an observation period of 9.2 years in the treated group and 8.2 years in the non-treatment group. The risk ratio of HCC development between the 2 groups was now 0.256 (95% CI 0.125–0.522), still significant but increased from the previous value. In the treatment group, HCC developed mostly in those who failed to achieve a sustained virologic response. The risk ratio was 0.250 (95% CI 0.124–0.505) for deterioration of liver function (to Child-Pugh B), and 0.135 (95% CI 0.049–0.372) for death. The last figure indicates the significant effect of IFN therapy on survival of chronic hepatitis C patients with cirrhosis.

Recently, a large-scale RCT, called the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) study, was performed in the USA. There was no significant difference in the incidence of HCC between patients assigned to receive Peg-IFN alfa-2a 90 μg/week as maintenance therapy (n = 495) and those assigned to no treatment (n = 510) [20]. The cumulative incidence of HCC 5 years after randomization was almost identical in

Table 1. Annual incidence of hepatocellular carcinoma in the non-IFN-treatment group

Fibrosis stage	Incidence
F0/1	0.45 (3/160)
F2	1.99 (11/164)
F3	5.34 (13/59)
F4	7.88 (32/107)

Table 2. Hazard ratio of HCC development according to IFN response

	Hazard ratio (95% CI)	p value
No IFN treatment	1	
IFN treatment	0.516 (0.358–0.742)	<0.001
With SVR	0.197 (0.099–0.392)	<0.001
Without SVR	0.631 (0.434–0.918)	0.016

SVR = Sustained virologic response.

Table 3. Annual incidence of hepatocellular carcinoma in the group with a sustained virological response

Fibrosis stage	Incidence
F0/1	0.11 (1/257)
F2	0.10 (1/316)
F3	1.29 (7/163)
F4	0.49 (1/53)

Table 4. Annual incidence of hepatocellular carcinoma in the group without a sustained virological response

Fibrosis stage	Incidence
F0/1	0.07 (1/443)
F2	0.78 (15/568)
F3	2.20 (30/389)
F4	5.32 (30/168)

the two arms: 5.4% in the treatment group and 5.0% in controls. The reason for the discrepant results between the Japanese and USA studies needs further clarification, together with analysis of the difference in incidence rates of HCC among cirrhotic patients in the 2 countries.

Yoshida et al. [13] reported a large-scale cohort study called IHIT (Inhibition of Hepatocarcinogenesis by IFN Therapy). The total number of patients was 2,890, with 2,400 of them receiving IFN. HCC developed in 89/2,400 treated patients and 59/490 untreated patients during a mean follow-up period of 4.3 years. In multivariate analysis, the adjusted risk ratio of HCC development for IFN treatment versus non-treatment was 0.52 (95% CI 0.36–0.74), reduced by half with IFN therapy. Consecutive patients who underwent liver biopsy were included in this multicenter study. The annual incidence rates of HCC in the non-treatment group, stratified by the stage of liver fibrosis, was shown in table 1, which may serve as the incidence rate of HCC in the natural course of chronic hepatitis C in Japan. The annual incidence rate among patients with fibrosis at F4 stage (cirrhosis) was as high as 7.9%, and that among patients at F3 was 5.3%. HCC developed even in patients at F2, although there is the possibility that liver fibrosis progressed during the follow-up period. As discussed in more detail below, on average the liver fibrosis stage progresses one stage in 10 years. The risk of HCC development at stage F4 was 24-fold higher than that at F1.

When the reduction in HCC incidence was analyzed separately according to the responses to IFN therapy, the risk ratio compared to non-treatment, calculated with multivariate Cox proportional regression model adjusting for age, sex, and fibrosis stages, was 0.20 (95% CI 0.01–0.39) in patients who showed a sustained virologic response (789/2,357, 33.5%) and 0.63 (95% CI 0.43–0.92) in patients who did not show a sustained virologic response to IFN (1,525/2,353, 66.5%; table 2). The risk reduction was notable especially at stage F4 (tables 3, 4). Even when HCV was not eliminated, the incidence of HCC was reduced compared to the non-treatment group (table 4). The possible mechanisms of this phenomenon are: (1) suppression of virus amplification and inflammation during IFN administration, and (2) the presence of biochemical responders, i.e. those who showed normalization of serum ALT levels in spite of continuing viremia after the cessation of IFN. However, these effects may become less important in the long run, especially because active hepatitis often recrudesces in biochemical responders. Indeed, the difference in HCC incidence was not found to be significant between untreated patients and those showing continued viremia in a follow-up analysis of the cohort.

Table 5. Cause of death

	Untreated (n = 459)	IFN-treated		
		all (n = 2,430)	with SVR (n = 817)	without SVR (n = 1,613)
Deaths, n	30	56	7	49
Liver related, n	23 (77%)	35 (63%)	2 (29%)	33 (67%)
Liver unrelated, n	7 (23%)	21 (37%)	5 (71%)	16 (33%)

SVR = Sustained virologic response.

There are two meta-analysis papers on the effect of IFN therapy in chronic hepatitis C patients with cirrhosis. Papatheodoridis et al. [21] selected 11 papers that reported HCC development after IFN therapy in chronic hepatitis C patients with cirrhosis together with untreated controls. The summary odds ratio of HCC development between no treatment and IFN treatment was 3.0 (95% CI 2.3–3.9), indicating a significant reduction in HCC among IFN-treated patients. Camma et al. [22] selected 14 papers and reported that the summary risk difference of HCC development was –13% (95% CI –8.3 to –17.2) in the IFN treatment group compared to the non-treatment group. Because in both papers the observation time was not considered in these meta-analyses, the clinical significance of risk difference was not clear.

Resolution of Liver Fibrosis

Progression of liver fibrosis was once thought to be an irreversible phenomenon, and therefore liver cirrhosis was the terminal phase of chronic liver diseases. These statements may have been true when there were no curative treatments for chronic hepatitis. Since the advent of antiviral therapy with IFN, however, there has been great interest in the possibility of resolving liver fibrosis. After all, fibrogenesis is a dynamic process consisting of both synthesis and degeneration of collagen.

In the above-mentioned IHIT study, the sequential changes in liver histology were analyzed using paired biopsy in a subset of patients [23]: 183 patients who achieved a sustained virologic response; 304 patients who were treated but did not achieve a sustained virologic response, and 106 patients who were not treated with IFN. The mean interval between the two liver biopsies was 3.7 years. Liver fibrosis was staged on a 0–4 scale according to the classification of Desmet et al.: F0 = no fibrosis; F1 = mild fibrosis; F2 = moderate fibrosis; F3 = severe fibrosis, and F4 = cirrhosis. In the non-treatment group, amelioration of fibrosis was seen only in 5 patients (5%) while progression was seen in 40 patients (38%). Importantly, 3 of 12 patients at stage F3 initially and 6 of 35 patients at F2 initially progressed to F4, cirrhosis. If we calculate the fibrosis progression rate simply by dividing the changes in liver fibrosis stage by the time interval, it is 0.10 ± 0.02 units/year. In the natural course of chronic hepatitis C, it will take about 10 years on average to progress one stage in liver fibrosis.

In patients showing a sustained virologic response, in contrast, liver fibrosis ameliorated in 108 of 183 patients (59%) and exacerbated only in 2 patients (1%). Most importantly, 11 of 24 patients who had been diagnosed with cirrhosis were found non-cirrhotic at the second biopsy. The rate of fibrosis regression after a sustained virologic response to IFN was calculated to be 0.28 ± 0.03 units/year.

Improvement in Survival

Cirrhosis develops in 20–30% of patients with chronic hepatitis C and usually remains asymptomatic for many years [3]. Nevertheless, serious sequelae such as HCC, liver failure, and variceal rupture may occur, accounting for an annual mortality of 2–5% [24]. To assess the importance of IFN therapy, its effect on overall survival must be evaluated. During the follow-up period in the above-mentioned IHIT study, a total of 86 patients died [25]. The cause of death is summarized in table 5 as grouped by treatment and responses. Approximately 80% of patients in the non-treatment group died of liver-related causes, whereas few patients died of liver-related causes among sustained virologic responders. In the natural course of chronic hepatitis C in Japan, HCC is by far the most important cause of death. Since the incidence of HCC is reduced in patients treated with IFN, especially those showing a sustained virologic response, beneficial effects of IFN therapy on overall survival can be expected.

Yoshida et al. [25] demonstrated the effect of antiviral therapy on survival by calculating a standardized mortality ratio (SMR). SMR is calculated as the number of observed deaths in a group of patients divided by the number of deaths expected based on gender- and age-ranked mortality in the reference population, in this case the general Japanese population. If the 95% confidence interval does not include 1, a significant difference from the reference population is indicated. In the IHIT study, the SMR was 1.9 and 95% CI was 1.3–2.8 in the non-treat-

ment group, indicating that mortality was significantly higher than in the general population, while it was 0.9 (95% CI 0.7–1.1) in the IFN-treated group, indicating no significant difference. The SMR for liver-related death was high among the untreated patients (SMR 13.5; 95% CI 8.6–20.3) and also among the IFN-treated patients as a whole (SMR 4.7; 95% CI 3.3–6.5), but not in patients showing a sustained virologic response (SMR 0.8; 95% CI 0.1–3.0). These data indicate that IFN therapy improves life expectancy by preventing liver-related deaths. The effect is much stronger among sustained virologic responders.

Tertiary Prevention of HCC

The short-term prognosis of HCC patients has much improved recently due to advances in early diagnosis and treatment. However, the long-term prognosis is as yet far from satisfactory, as indicated by the fact that overall survival at 10 years after apparently curative treatment of HCC is as low as 22–35%. The slope of cumulative survival curves of HCC patients after treatment does not level out over time, in contrast to the fact that the slope of the cumulative survival curve levels out in about 5 years after relatively curative treatment of most other malignancies. In other words, HCC is rarely curatively treated, and the major reason for this phenomenon is the extremely frequent recurrence of HCC even after apparently curative treatment, either local ablation or surgical resection. HCC nodules can be completely removed by surgical resection or ablation therapies. Microscopic intrahepatic metastasis, which will result in early-phase recurrence, is not infrequent, but the risk can be reduced by detecting the primary HCC at an early stage. Nevertheless, recurrence is distressingly frequent after apparently curative surgery or ablation. The recurrence rate does not decline with time, suggesting that most cases of late-phase recurrence are due to metachronous multicentric or de novo carcinogenesis. This is quite understandable because the remaining liver, often cirrhotic, is still at a high risk of hepatocarcinogenesis. The rate of metachronous recurrence after complete resection or ablation is estimated to be as high as 20%/year. An ideal solution to this difficulty will be liver transplantation. At least theoretically, liver transplantation provides each patient with a cancer-free normal liver without risk of multicentric carcinogenesis. Currently, when the extent is contained within certain criteria and extrahepatic metastasis is ruled out, the presence of HCC is not considered a contraindication but rather an indication for liver transplantation. However, the feasibility of liver transplantation is limited worldwide by the scarcity of tissue donors. Living donor liver transplantation is an alternative choice but not always feasible. Moreover, in both cadaveric and living donor liver transplantation, the control of hepatitis viruses, especially HCV, is difficult with a postoperative immunosuppressant.

Another approach will be treating both HCC and viral hepatitis. Several small-size RCTs, performed in Japan or Taiwan, showed that the incidence of recurrence was reduced in HCV-related HCC by IFN therapy subsequent to initial HCC treatment [26, 27]. Other RCTs, also performed in Japan and Taiwan, failed to find a significant delay in the first recurrence with IFN therapy, but the second or third recurrence was significantly reduced especially in sustained responders, and overall survival was improved [28, 29]. These data are compatible with the hypothesis that de novo carcinogenesis was prevented by successful antiviral therapy. On the other hand, 2 reports on long-term observation of recurrence after IFN following HCC treatment showed that the recurrence rate in IFN-treated patients increased over time, suggesting that the growth of residual microscopic tumors had been delayed by IFN (in fact, the 2 presumed mechanisms are not necessarily mutually exclusive) [30]. Most of these studies used IFN monotherapy and suffered from low sustained response rates because most patients had advanced fibrosis or cirrhosis. Preventive effects of IFN on HCC recurrence are yet to be reevaluated by using current more efficient protocols. With IFN therapies with improved efficacy, we can anticipate more favorable outcomes.

Disclosure Statement

The authors declare that they have no financial conflict of interest.

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