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REVIEW

Chemoprevention of hepatocellular carcinoma in patients with hepatitis C virus related cirrhosis

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Abstract

Interferon (IFN) therapy has been reported to decrease the risk of hepatocellular carcinoma (HCC) and improve survival by preventing liver-related deaths in patients with chronic hepatitis C virus (HCV) infection, while the role of IFN therapy on the natural history of hepatitis C related cirrhosis is still under debate. The ideal goal of therapy is to prevent the progression into end-stage disease. The use of IFN in patients with HCV compensated cirrhosis reduces the negative clinical evolution independently of the type of laboratoristic and virological response. In our experience, IFN therapy in HCV compensated cirrhosis is barely useful in prevention of HCC, as cirrhosis itself represents a risk of cancer. Some authors noted that IFN treatment reduces the risk of HCC independently of the virological response. It would probably be interesting to evaluate the efficacy of weekly low-dose pegylated (PEG)-IFN therapy in patients with HCV cirrhosis and to assess potential benefits of long-term PEG-IFN plus Ribavirin treatment.

Key words: Chemoprevention; Cirrhosis; Hepatitis C virus; Hepatocellular carcinoma

Core tip: Interferon (IFN) therapy has been reported to decrease the risk of hepatocellular carcinoma (HCC) and improve survival. The use of IFN in patients with hepatitis C virus (HCV) compensated cirrhosis reduces the negative clinical evolution independently of the type of the laboratoristic and virological response. In our experience, IFN therapy in HCV compensated cirrhosis is barely useful in the prevention of HCC, as cirrhosis itself represents a risk of cancer. It would probably be interesting to evaluate the efficacy of weekly low-dose pegylated (PEG)-IFN therapy in patients with HCV cirrhosis and to assess potential benefits of long-term PEG-IFN plus Ribavirin treatment.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer death in the world[1]. The most current statistics available estimate 609000 deaths globally from this disease in 2004[2].

The risk of HCC in patients with chronic hepatitis C is highest in patients who have established cirrhosis, in whom the incidence of HCC is between 2%-8% per year[3].

There is a single prospective population-based study of the risk of HCC in hepatitis C virus (HCV) patients. In this study of 12008 men, being anti-HCV-positive conferred a 20-fold increased risk of HCC compared with anti-HCV-negative subjects. Hepatitis C infected patients who do not have cirrhosis have a much lower risk

of developing HCC[3].

NATURAL HISTORY

The overall natural history of HCV infection is somewhat variable and the long-term risks are difficult to estimate due to the extended periods of time involved. Approximately 20% of subjects with post-transfusion chronic hepatitis C developed histological evidence of cirrhosis in the first 10 years after transfusion[4].

Factors that promote progression of chronic hepatitis include alcohol consumption, male sex, age over 40 years at the time of infection, and severe histology at the time of initial diagnosis. Co-infection with human immunodeficiency virus and/or hepatitis B virus (HBV) has also been associated with premature and more severe liver disease[5].

The risk of developing HCC in HCV patients can be estimated from the results of natural history studies of HCV infection and studies on the development of HCC in patients with HCV-related cirrhosis. If 60% of patients exposed to HCV develop a chronic infection and 20% of them develop cirrhosis within 10 years, it means that approximately 12% of all these patients will be at high risk for HCC.

Any chronic inflammatory liver disease has the potential to induce HCC but the pathophysiological process most commonly associated with the disease is cirrhosis, found in up to 80% of cases. However, knowledge of all possible sources is important, considering that 20% of cases are due to non cirrhotic, non viral causes[6].

Viral, environmental, hereditary and dysmetabolic causes of cirrhosis certainly have a strong correlation with HCC. HBV infection is the leading cause of chronic liver disease and HCC around the world. HCV-RNA was found in about 65% of hepatitis B surface antigen-negative patients at diagnosis of HCC. Patients who develop cirrhosis may stay in a compensated state or may decompensate with ascites, jaundice, hepatorenal syndrome, hepatic encephalopathy or variceal bleeding.

Patients with compensated cirrhosis had a 5 year mortality of 50% and a 10 year mortality of 70%. The probability of decompensated cirrhosis was 18% at 5 years and 29% after 10 years of cirrhosis[7].

The prognosis of HCC remains poor for the majority of patients who present with advanced disease. Treatment options depend on the tumor size, the number of lesions and the stage of cancer. Thirty percent of patients are candidates for surgical resection and the recurrence rate is about 50% at 3 years. In 2008, a major breakthrough in the treatment of advanced HCC was announced in the form of sorafenib (multikinase inhibitor) which was shown to increase the median overall survival from 7.9 to 10.7 mo without severe side effects in a randomized, placebo-controlled phase-Ⅲ trial. However, sorafenib did not delay time to symptomatic progression[8,9].

HEPATOCARCINOGENESIS AND HCV

HCV is a noncytopathic virus of the Flaviviridae family. The HCV single-stranded RNA genome encodes nonstructural proteins (NS2, NS3, NS4A, NS4B and NS5B), which associate with endoplasmic reticulum membrane to form the viral replicase and the viral envelope proteins (E1 and E2).

The precise mechanism by which HCV infection results in HCC is not well known. After hepatic injury incurred by HCV, there is necrosis followed by hepatocyte proliferation. Continuous cycles of this destructive-regenerative process foster a chronic liver disease condition that culminates in liver cirrhosis.

Probably cirrhosis itself is responsible for malignant transformation of hepatocytes; in cirrhosis inflammation, in fact, the increased cellular turnover and fibrosis favor mutations in hepatocytes and the eventual development of HCC[10-12].

It has been noted that the HCV core protein has some potential direct carcinogenic effects *in vitro*, including the transformation of rat embryo fibroblasts to the malignant phenotype and the suppression of apoptotic cell death in culture. In addition, HCV-RNA and/or core protein have been suggested to impair dendritic cell functions that are important for T-cell activation[9]. Furthermore, the HCV core protein and the NS5A nonstructural proteins have been implicated in the evasion from immune-mediated cell killing by interacting with various factors involved in this process. In addition, the protease activity of NS3 is enhanced by the NS4A cofactor and the NS3-4A protease activity is involved in blocking the ability of the host cell to mount an innate antiviral response[13,14].

HCV core protein can activate the mitogen-activated protein kinase signaling pathway, modulate cell proliferation, and promote the induction of reactive oxygen species.

Moreover, HCV core-E1-E2 transgenic mice develop significantly larger tumors than transgenic mice expressing core alone or nontransgenic mice. The accelerated tumor phenotype is attributable to suppression of apoptosis[15].

At the molecular level, the interaction between oncogenes, tumor suppressor genes and several growth factors may play an additional role in HCC development.

NS5A has been shown to interact with and inactivate p53 by sequestration to the perinuclear membrane, thereby affecting the p53-regulated pathways that control cell-cycle progression, cellular survival, response to hypoxic and genotypic stresses, and tumor angiogenesis.

A p73 overexpression and nuclear accumulation in HCV-associated HCC has been observed. The *p73* gene activates the transcription of p53-responsive genes and inhibits cell growth by inducing apoptosis. p73 seems to be strongly involved in hepatocarcinogenesis, probably through a protein-protein interaction with the HCV proteins[16].

Loss and/or mutation of p53 and genomic instability also characterize hepatocarcinogenesis. p53 loss and/or mutation is shown to occur during progression to HCC; however, there is some evidence that loss and mutation of p53 might also occur in the initial stages of hepatocarcinogenesis[9,16].

Telomere shortening is a feature of HCV chronic liver disease and cirrhosis and telomerase reactivation has been associated with HCV hepatocarcinogenesis[9].

There is a strong activation of telomerase reverse transcriptase in nearly 90% of human HCCs. Telomerase reactivation has been suggested to promote HCC progression (increased micro-vessel density and HCC recurrence after resection)[9].

Alcohol is an important cofactor in patients with HCV infection and it has been estimated that 30% of patients with alcoholic liver disease are infected with HCV[3]. Subjects with both HCV infection and alcohol addiction have been shown to develop more severe fibrosis and have higher rates of cirrhosis and HCC than non-drinkers. The risk for developing HCC has also been shown to increase as levels of alcohol intake rise. The dominant mechanism for synergism between alcohol and HCV infection appears to be increased oxidative stress[9].

Data linking being overweight/obesity to liver disease and HCC are well established. The risk of incident HCC is 3 times higher in patients with a body mass index of 30 kg/m^2[17].

Finally, genetic polymorphisms are important risk factors for liver disease evolution: genetic variations involved in oxidative stress, controlling hepatic lipid storage, modulating endotoxin inflammation and polymorphic variants of fibrosis associated genes are correlated with fast evolution towards cirrhosis in patients with chronic HCV[11].

ROLE OF INTERFERON TREATMENT IN COMPENSATED CIRRHOSIS

Tremendous efforts have improved the understanding of the pathogenesis and treatments of HCC but relatively little effort has been made to develop effective chemoprevention of HCC[8].

Chemoprevention is defined as the use of natural or synthetic agents to reverse, suppress or prevent premalignant conditions from progressing to invasive cancer. Chemoprevention may be classified into 3 categories: primary (preventing cancer in healthy subjects), secondary (preventing cancer in subjects with premalignant conditions, for example, the presence of cirrhosis) and tertiary (preventing recurrence)[18].

The ideal goal of secondary chemoprevention is to eradicate HCV at the beginning of the disease and to prevent progression into end-stage disease and HCC. Interferon (IFN) therapy has been reported to decrease the risk of HCC and improve survival by preventing liver-related deaths in patients with chronic HCV infection (mainly in those with a complete and sustained response), while the role of IFN therapy on the natural history of HCV related cirrhosis and on chemoprevention of HCC is still under debate.

In our experience[19], we conducted an experimental research involving patients with compensated HCV-related cirrhosis (Child-Pugh A) histologically confirmed, abnormal alanine-aminotransferase (ALT) values and serum HCV-RNA positivity. IFN therapy *vs* no therapy have been compared. Qualitative and quantitative detection of HCV-RNA was performed with the Cobas Amplicor HCV Test, version 2.0 and the Cobas Amplicor HCV Monitor, version 2.0 (Roche Diagnostics, Branchburg, NJ, United States). The qualitative assay is able to detect HCV-RNA at a concentration of 50 IU/mL, with a positive rate of 95% or greater. The Cobas Amplicor HCV Monitor, version 2.0 has a dynamic range between 600 and 8.5 × 10 IU/mL. HCV genotyping was performed by sequencing of the 5'-untranslated regions (5'UTR) (Visible Genetics Tru-Gene Hepatitis Assay, Toronto, Canada). The phylogenetic analysis of the 5'UTR nucleoside sequence, together with appropriate homologous references of the main subtype sequences, permitted genotyping[19-21].

In both groups we investigated the incidence of the following negative events: cirrhosis worsening (passage from Child A to Child B or C), HCC onset, and death or orthotopic liver transplantation (OLT).

A cohort of 122 patients, prospectively enrolled, was retrospectively analyzed to assess the effect of IFN therapy (mean follow-up: 96 ± 18.3 mo). Only patients who had received a blood transfusion before 1980 were selected. Fifty-nine patients (mean age: 55.3 ± 7 years) (mean follow-up 96.5 ± 18 mo) received IFN (3 MU three times a week for 12 mo), 8 stopped therapy for side effects; 71 patients did not receive IFN (mean age: 56.8 ± 8 years) (mean follow-up 95.4 ± 17.8 mo).

Baseline patient characteristics were similar, including age, sex, HCV-RNA genotype, liver function tests, alpha-fetoprotein levels, leukocyte and platelet counts, and alcohol consumption.

Response to therapy was assessed as follows: a sustained virological response (SVR) was defined as the absence of serum HCV-RNA for at least 6 mo after interferon-alpha therapy; a sustained biochemical response was defined as a decrease in serum ALT activity to within the reference range but with persistently detectable serum HCV-RNA. Non-response was defined as persistence/relapse of HCV-RNA and no decrease/relapse in ALT activity at the end of the therapy[19].

All patients were subjected to ultrasound follow-up investigations, performed at 4-6 mo intervals. Laboratoristic exams were carried out at all clinical visits: every 15-30 d (in the group of treated patients) or every 4-6 mo (in the group of untreated patients). If necessary, a spiral CT, angiography and endoscopic examination were performed and in suspected HCC, fine needle biopsy under sonographic guidance was carried out.

Final results showed that treated patients exhibited

Table 1 Worst evolution (negative events altogether evaluated) and hepatocellular carcinoma incidence in interferon treated patients *n* (%)

	Worst evolution	HCC
NR	13/22 (59.0)	7/22 (31.8)
SR	3/11 (27.2)[b]	3/11 (27.2)
RR	7/18 (38.8)[b]	5/18 (27.7)
Not treated	63/71 (88.7)[b]	24/71 (33.8)

[b]$P < 0.01$ *vs* non responder (NR). SR: Sustained responder; RR: Relapse responder; HCC: Hepatocellular carcinoma.

negative events in 45% of the cases (23/51) and untreated patients in 88.73% (63/71) ($P < 0.0001$).

In the IFN treated group, 6 patients (11.76%) showed worsening cirrhosis according to Child's classification, 15 patients (29.4%) developed HCC, 1 patient died, and 1 patient underwent liver transplantation. In the IFN untreated group, 27 patients (38%) showed worsening cirrhosis (*vs* treated patients $P = 0.003$), 24 developed HCC (*vs* treated patients $P = 0.752$) and 12 died or underwent OLT (16.9% *vs* treated patients $P = 0.054$) (9 died and 3 underwent OLT).

A complete and sustained response (SR) to IFN was observed in 11 of the 51 patients treated (21.5%), a relapse (RR) was observed in 18 cases (35.2%) and no response (NR) in 22 cases (43.1%).

Data confirm that, in relationship to the type of response to therapy, a worse evolution occurred (negative events altogether evaluated) in NR (13/22, 59%) rather than in SR (3/11, 27.2%) and RR (7/18, 38.8%) ($P < 0.01$). It is important to underline that untreated patients developed more negative events (63/71, 88.7%) than NR patients (13/22, 59%) ($P < 0.01$) (Table 1).

No particular differences have been noticed in relationship to HCC onset (SR 3/11, 27.2%; RR 5/18, 27.7%; NR 7/22, 31.8%; no treated patients 24/71, 33.8%) ($P > 0.05$) (Table 1).

Afterwards, we evidenced that the cumulative probabilities of developing HCC were not significantly higher in untreated patients compared with IFN treated cases when assessed by the Kaplan-Meier and log-rank test ($P > 0.05$)[22].

DISCUSSION

There is evidence that the use of IFN as a therapy for chronic hepatitis may slacken the natural history of the pathology, particularly in patients who have a long-term sustained response[19,23-26].

Meta-analysis demonstrated a decrease of HCC incidence in treated patients in comparison with those untreated and other studies evidenced a lower risk of cancer in subjects with virus clearance in comparison with non-responders[27,28].

The use of IFN in viral cirrhosis is controversial with respect to its cost effectiveness[18,29]. A remarkable heterogeneity among the study was found and the magnitude of the overall effect is low[19,22,30-40] (Table 2).

From our data, it seems that the administration of IFN in HCV compensated cirrhosis is barely useful in the prevention of HCC when cirrhotic structural alterations arise as cirrhosis itself represents a risk factor for HCC.

In 1995, a small randomized clinical trial showed a decrease in the incidence of HCC in subjects with HCV cirrhosis treated with IFN-alpha compared with untreated controls[30,31]. In the wake of this study, several controlled trials were performed[30,41]. Three meta-analyses evaluated whether IFN reduces the incidence of HCC in patients with HCV-related cirrhosis. The most recent review shows that IFN seemingly decreased the HCC rate in all but one of the 20 studies included in the meta-analysis. The rate difference between IFN-treated patients and controls of each trial ranged from -33.3% to +3.9%. The pooled estimate of the treatment effect was significantly in favor of a preventive effectiveness of IFN ($P < 0.00001$). A remarkable heterogeneity among the studies ($P > 0.0001$) was found. The most prominent heterogeneity was in the difference of magnitude of the treatment effect on the risk of cancer[30].

However, the magnitude of the overall effect is low and the observed benefit might be due to spurious associations. The preventive effect is stronger among sustained responders to IFN, which intrinsically represents a small proportion of all cirrhotic patients[30].

Thereafter, three observational cohort studies, 2 prospective studies conducted in Japan[30,42] and Taiwan[30,34] and one retrospective study conducted in Italy[30,35], confirmed that the efficacy of IFN in the chemoprevention of HCC is exclusively linked to the achievement of a SVR, whereas no benefit in reducing HCC development has been observed in non-responder patients[30].

Some authors noted that treatment with IFN reduces the risk of HCC independently of the virological response[31,43,44]. The reason is unclear, although it has been suggested that the anti-proliferative activity or other properties[45] of IFN may be responsible. In accordance with Kowdley[46], it is perplexing that only 6 or 12 mo of therapy can produce this benefit. Moreover, some authors reported some cases of HCC onset after 3-6 years of SVR in patients treated with IFN, with moderate or severe stage of liver fibrosis before IFN treatment[47-49]. Nojiri *et al*[50] retrospectively studied 5 patients who had developed HCC more than 10 years after the termination of IFN therapy. These patients had achieved a long-term SVR. The authors concluded that HCV patients who respond to IFN therapy should undergo long-term follow-up, even after a SVR, especially if they have an advanced histological fibrosis stage or higher serum ALT or other risk factors.

Mazzaferro *et al*[39] reported that IFN does not affect overall prevention of HCC recurrence after resection and Craxì *et al*[18] evidenced that in the setting of secondary chemoprevention, literature data pooling suggests a slight preventive effect of IFN on HCC development in patients with HCV-related cirrhosis. The observed benefit might be due to spurious associations.

Kubo *et al*[51] declared that postoperative IFN-alpha therapy appears to decrease the incidence of recurrence

Table 2 Features of the studies on cirrhotic patients

Type study	Follow-up (mo)	IFN (wk)	Sample size	Mean age (yr)	RR	Ref.
RCT	24-86	6 MU tiw (12-24)	T 45/C45	55	-0.4	[31]
NRCT/P	12-71	3 MU tiw (52)	T193/C91	57	-0.1	[32]
NRCT/P	60-84	6 MU tiw (26)	T82/C81	56	2	[33]
NRCT/P	43	3 MU tiw (65)	T103/C59	57	-0.05	[34]
RCT	60	6 MU tiw (18) 3 MU tiw (18)	T38/C23	57	> 1	[35]
P	55	1 MU tiw (12) 3 MU tiw (12) 6 MU tiw (12) 9 MU tiw (12)	T72/C72	58	-0.2	[36]
R	96	3 MU tiw (12)	T52/C71	56	> 1	[19]
P	60	6 MU/mo (4) 3 MU/mo (44)	T41/C30	56	-0.1	[37]
R	96	3 MU tiw (12)	T52/C71	56	> 1	[22]
P	60	3-6 MU tiw plus Ribavirin (2-48)	T1057/C562	56	-0.05	[38]
RCT	45	3 MU tiw (48) (post-resection)	T76/C74	66	> 1	[39]
P	96	6 MU tiw (24-48)	T82/T81	57	-0.04	[40]

RCT: Randomized controlled trial; NRCT: Non randomized controlled trial; P: Prospective; R: Retrospective; IFN: Interferon; T: Patients treated; C: Controls; RR: Relative risk.

after resection of HCV-related hepatocellular carcinoma, and also in patients with persistently detectable serum HCV-RNA.

It is important to underline how the management of dysmetabolism, diet and exercise therapy can improve BMI, liver histology and, therefore, the response to pegylated (PEG) interferon and Ribavirin, and decreases the incidence of HCC[52,53].

In fact, it is well known how insulin resistance and adipocytokine disorders may be implicated in HCV hepatocarcinogenesis[54,55].

CONCLUSION

According to Cammà *et al*[56], IFN prevents or delays the development of HCC in patients with HCV-related cirrhosis but the magnitude of the overall effect is low and the observed benefit might be due to spurious associations. The preventive effect is stronger among a sustained virological response to IFN. The cost-effectiveness of treatment for chronic hepatitis C is substantially acceptable[57-59]; in particular, Kawaguchi *et al*[60] affirm that the cost-effectiveness of long-term treatment could be lower than that of patients never treated with IFN, according to their long-term follow-up assessment. More recently, extended analysis of the Hepatitis C Antiviral Long-term Treatment against Cirrhosis Trial[61] showed that long-term PEG-IFN therapy does not reduce the incidence of HCC among patients with advanced hepatitis C who did not achieve SVR. Patients with cirrhosis who received PEG-IFN treatment (PEG-IFNα-2a 90 microg/weekly) for 3.5 years and followed up for a median of 6.1 (maximum, 8.7) years had a lower risk of HCC than controls[1].

In our experience, maintenance therapy in non-responder patients slows down the hepatic fibrotic evolution[62]. Probably, in relationship to the ability of IFN to inhibit the growth of pre-neoplastic cells[63-65], it would be interesting to evaluate the efficacy of weekly low-dose PEG-IFN therapy in patients with HCV cirrhosis and to assess potential benefits of long-term PEG-IFN plus Ribavirin treatment.

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