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Cirrhotic patients are still at risk of developing hepatocellular carcinoma despite Interferon-induced sustained virological response

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Abstract. – INTRODUCTION: Hepatitis C virus (HCV) infection is a common cause of chronic liver disease and hepatocellular carcinoma (HCC). The prevalence of HCC significantly declines among patients achieving a sustained virological response (SVR) after antiviral therapy with pegylated(PEG)-interferon (IFN) and ribavirin. However, up to 5% of patients with SVR may develop HCC.

PATIENTS AND METHODS: We investigated the epidemiological, clinical, biochemical and virological characteristics of a small cohort of patients with chronic hepatitis C (CHC) who developed HCC after being successfully treated with PEG-IFN-α and ribavirin.

RESULTS: Between September 2000 and January 2003, 598 patients with CHC underwent a complete course of treatment with PEG-IFN-α and ribavirin; 221 out of 598 (37%) patients obtained a SVR. Throughout the 10-year post-treatment follow up, 13 of 221 (5.8%) SVR patients developed HCC. All 13 patients were male and were affected with Child A liver cirrhosis; in addition, at baseline they were significantly older ($p < 0.05$) and had higher alpha-fetoprotein levels ($p < 0.05$) in comparison with those who did not develop HCC. Nine patients (69.3%) developed HCC within the first 3 years after antiviral treatment completion, one patient (7.7%) between 3 and 5 years and 3 subjects (23%) between 5 and 10 years; 12 of 13 had a solitary lesion with a mean diameter of 2.5± 0.5 cm. Eleven cases (84.6%) underwent surgical resection, one (7.7%) received liver transplantation, one (7.7%) received palliative care.

CONCLUSIONS: The risk of developing HCC after achieving SVR persists in patients with HCV-related cirrhosis. As a consequence, these patients should continue to undergo long-term surveillance for HCC, in order to early detect and treat it.

Key Words:
Chronic hepatitis C, Cirrhosis, Hepatocellular carcinoma, HCV, Interferon, Sustained virological response.

Introduction

Hepatitis C virus (HCV) infection is a common cause of chronic liver disease and hepatocellular carcinoma (HCC). Approximately sixty to 70% cases of HCC are associated with HCV infection[1]. The annual incidence of HCC ranges from 2 to 5% of all cirrhotic patients[1]. In patients with chronic hepatitis C (CHC) the occurrence of HCC has been associated with the degree and severity of liver fibrosis[2]. Before the introduction of triple antiviral treatment (including the most recent protease inhibitors boceprevir and telaprevir), standard therapy of CHC was based on the combination of pegylated (PEG)-interferon(IFN)-α and ribavirin for as long as 12 months in genotype 1-infected patients and 6 months in the so-called "easy-to-treat" genotypes, such as genotype 2 and (to a lesser extent) genotype 3[3].

It has been reported that IFN therapy not only improves hepatic inflammation and fibrosis, but also leads to a reduction in the incidence of HCC, with particular reference to those patients achieving a sustained virological response (SVR)[4,5]. Nevertheless, HCC has been shown to still occur despite antiviral therapy up to 18 years after completing IFN therapy[4-8]. Risk factors for HCC in patients with CHC include male sex, age older than 50 years and the presence of cirrhosis. These risk factors have been also associated with the development of HCC among patients experiencing SVR[4-10]. Comprehensively, the number of patients who develop HCC after achieving SVR is limited and the magnitude of this residual risk has not been fully clarified.

In the present study, we investigated the epidemiological, clinical, biochemical and virological characteristics of a small cohort of patients

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with CHC who developed HCC after being successfully treated with PEG-IFN-α and ribavirin.

Patients and Methods

In January 2014 we revised the medical records of all patients with CHC who underwent a complete (12 months for genotype 1 and at least 6 months for genotype 2 and 3) course of antiviral treatment with PEG-IFN-α and ribavirin and obtained a SVR as assessed by a negative serum HCV RNA as long as 12 months after the end of therapy.

Subsequently, among patients who obtained SVR we selected those with a minimum of 10 years post-treatment follow up: thus, the analysis was conducted on those who successfully received PEG-IFN-α and ribavirin between September 2000 and January 2003.

We excluded patients who developed HCC before completing antiviral therapy, those whose clinical, virological or biochemical data were incomplete or unavailable, those who lacked an adequate post-treatment follow up in terms of duration and regularity, those positive for hepatitis B surface antigen and those with risk factors for HCC other than HCV infection (autoimmune diseases, exposure to aflatoxins, non alcoholic fatty liver disease).

Statistical analysis was carried out using the statistical software package SPSS version 17.0 (SPSS, Chicago, IL, USA). A two-tailed *p* value of less than 0.05 was considered significant. All quantitative variables were expressed as mean ± standard deviation (SD). The chi-square test and the Fisher's exact test were adopted for statistical comparisons.

Results

Between September 2000 and January 2003, 598 patients affected with histologically proven CHC underwent a complete course of treatment with PEG-IFN-α and ribavirin; 322 were infected with genotype 1 HCV, 144 had a genotype 2 infection and 134 had a genotype 3 infection. The treatment course lasted 12 months in 382 cases and 6 months in 100. Comprehensively, during this period 221 out of 598 (37%) patients obtained a SVR as assessed by a negative serum HCV RNA by polymerase chain reaction 12 months after the end of therapy.

The baseline epidemiological, clinical, biochemical, virological and histological characteristics of patients reaching SVR are described in Table I.

Throughout the 10-year post-treatment follow up 13 of 221 (5.8%) patients with SVR developed HCC.

Characteristics of Patients who Developed HCC

All 13 patients with SVR who developed HCC were male. They were significantly older than patients who did not develop HCC (68 ± 12 vs. 46 ± 16, $p < 0.05$). All patients had a genotype 1

Table I. Baseline epidemiological, biochemical, virological and histological characteristics of patients achieving sustained virological response

Patients' characteristics	N = 221
Age (years)	56 ± 19
Men/Women N(%)	130(59)/91(41)
Body mass index (kg/m2) >25 N(%)	75(34)
Gamma-glutamyl transpeptidase (IU/l)	58 ± 41
Alanine aminotransferase (IU/l)	78 ± 37
Platelet count (/μl)	111.000 ± 32.000
Albumin (g/dl)	3.8 ± 1
Alpha-fetoprotein (ng/ml)	25 ± 22
HCV RNA (IU/ml)	650.000 ± 120.000
HCV genotype 1-2-3 N(%)	41(19)/110(50)/70(31)
Fibrosis stage F1/F2/F3/F4 N(%)	20(9)/81(36)/59(27)/61(28)
Child-Pugh class among cirrhotic patients class A/B/C N(%)	55(90)/6(10)/0(0)

Data are expressed as mean ± standard deviation, except where otherwise noted.

Table I. Baseline characteristics of patients achieving SVR who developed hepatocellular carcinoma (HCC) and patients with SVR who resolved their infection without developing HCC during the 10-year post-treatment follow-up.

Patients' characteristics	Patients with SVR without HCC (N=208)	Patients with SVR who developed HCC (N=13)
Age (years)	46 ± 16*	68 ± 12*
Men/Women N (%)	117(56)/91(44)	13(100)*/0(0)
Body mass index (kg/m2) >25 N (%)	72(35)	3(23)
Gamma-glutamyl transpeptidase (IU/l)	60 ± 40	53 ± 31
Alanine aminotransferase (IU/l)	70 ± 39	79 ± 27
Platelet count (/μl)	115.000 ± 25.000	101.000 ± 32.000
Albumin (g/dl)	3.9 ± 1	3.1 ± 1.1
Alpha-fetoprotein (ng/ml)	6 ± 5.1*	39 ± 17*
HCV RNA (IU/ml)	710.000 ± 100.000	612.000 ± 98.000
HCV genotype 1-2-3 N (%)	28(13)/110(53)/70(34)	13(100)/0(0)/0(0)*
Fibrosis stage F1/F2/F3/F4 N (%)	20(10)/81(39)/59(28)/48(23)	0(0)/0(0)/0(0)/13(100)*
Child-Pugh class among cirrhotic patients class A/B/C N (%)	48(100)/0(0)/0(0)	7(54)/6(46)/0(0)

Data are expressed as mean ± standard deviation, except where otherwise noted. *Student's *t* test $p < 0.05$.

HCV infection. By the time of treatment initiation they were all affected with Child A liver cirrhosis as assessed by liver biopsy. Their baseline alpha-fetoprotein (AFP) levels were significantly higher than those of subjects who did not develop HCC (39 ± 17 vs. 6 ± 5.1, $p < 0.05$).

Nine patients (69.3%) developed HCC within the first 3 years after IFN treatment completion, one patient (7.7%) developed HCC between 3 and 5 years and 3 subjects (23%) between 5 and 10 years after completing antiviral therapy; 12 of 13 had a solitary lesion with a mean diameter of 2.5 ± 0.5 cm. One case showed multiple nodular lesions at the time of diagnosis.

Eleven cases (84.6%) underwent surgical resection, one (7.7%) received liver transplantation whereas one (7.7%) received palliative care.

Table II shows the baseline characteristics of patients who developed HCC and those who apparently resolved liver disease.

Discussion

Eradication of HCV infection has been associated with a significant lower incidence of liver-related complications and deaths[4]. The risk of HCC is reduced among patients with HCV who achieve SVR after antiviral therapy. In a meta-analysis of Singal et al[5], the authors found that patients achieving SVR had a reduced HCC risk in comparison with nonresponders (relative risk 0.25; 95% confidence interval 0.14-0.46). However, it has been reported that up to 5% of patients with SVR may develop HCC on long-term follow up[4-10]. In our study, 6% of patients achieving SVR experienced HCC during the 10-year post-treatment follow up.

Two distinct patterns of HCC development after SVR have been suggested. In one pattern, HCC may develop after the eradication of HCV, as a consequence of residual potential for hepatocarcinogenesis despite SVR; in this case, elevation of AFP after antiviral therapy may help identifying HCC in its early stages. The other pattern is associated with HCC lesions that are too small to be detected before and just after antiviral therapy and that are identified on imaging studies only during long-term follow up[11]. The majority of our patients developed HCC within the first 3 years after SVR, possibly indicating that HCC was already present but not big enough to be visualized. In keeping with our results, Sato et al[7] found that higher pretreatment AFP levels (> 10 ng/ml) independently predicted the risk of developing HCC within five years after having completed antiviral therapy. On the other hand, Izumi et al[9] reported that AFP post-IFN levels were correlated with the occurrence of HCC among patients achieving SVR. In particular, AFP levels > 6 ng/ml were reported to be associated with an increased risk for HCC.

In our cohort, male sex and older age were significantly associated with the development of HCC. Analogously, both Nagaoki et al[12] and Sato et al[7] reported that older age at HCV eradication

was a risk factor for HCC after SVR. In addition, patients who developed HCC had all F4 fibrosis at baseline, which is consistent with previous reports[6,7,9,10].

Our study is a retrospective study, so that causal relationships could not be established. In addition, it was conducted on a small cohort of patients, thus, limiting the statistical power of our analysis. Larger prospective studies are needed to identify the relationship between SVR and HCC and the best surveillance approach for this subgroup of patients, also because this kind of patients represent an old/new challenge for the oncologist and infectivologist[13-25]. In the next future also the support of molecular diagnostic tests should be useful to better select patients at risk of developing HCC.

Conclusions

The risk of developing HCC after achieving SVR persists in patients with HCV-related cirrhosis. As a consequence, these patients should continue to undergo long-term surveillance for HCC, in order to early detect and treat it.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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