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The efficacy and safety of pegylated interferon plus ribavirin combination therapy in chronic hepatitis c patients with hepatocellular carcinoma post curative therapies – A multicenter prospective trial

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Background & Aims: Evidence on the efficacy of antiviral treatment in chronic hepatitis C (CHC) patients with hepatocellular carcinoma (HCC) after curative treatment is scarce. We aimed to evaluate the efficacy and safety of pegylated interferon-alpha plus ribavirin (pegIFN/RBV) combination therapy in these patients, compared to cirrhotic patients.

Methods: This prospective, multicenter, case–control study recruited 82 consecutive CHC patients with HCC after curative management and 87 sex/age-matched cirrhotic patients. All patients received pegIFN-alpha-2a and weight-based RBV according to current treatment recommendations. The primary outcome measurement was sustained virological response (SVR, seronegative of hepatitis C virus RNA throughout the 6-month post-treatment follow-up period).

Results: The SVR rate was significantly lower in the HCC group compared to the cirrhosis group (48.8% vs 64.4%, $p = 0.04$). However, the significantly lower rate of SVR in the HCC group was observed among genotype-1 patients (33.3% vs 60.7%, $p = 0.005$) but not among genotype-2/3 patients (70.6% vs 71.0%, $p = 0.88$). In patients who achieved 80/80/80 adherence, there was no significant difference of SVR rate between groups (50.7% vs 64.2%, $p = 0.12$) Multivariate logistic regression analysis demonstrated that rapid virological response (viral clearance during the first 4 weeks of treatment, odds ratio = 22.1, $p < 0.001$) and adherence (odds ratio = 3.1, $p = 0.05$) were predictive factors associated with SVR, whilst previous occurrence of HCC was not associated with SVR (Odds ratio = 0.4, $p = 0.09$). The incidence of severe adverse events did not differ between the two groups.

Conclusions: The study proved the feasibility of pegIFN/RBV therapy with current treatment guidelines in CHC patients after successful eradication of HCC, with careful monitoring.

Keywords: Hepatitis C virus; Pegylated interferon-alpha; Ribavirin; Hepatocellular carcinoma.

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Abbreviations: HCV, hepatitis C virus; CHC, chronic HCV infection; HCC, hepatocellular carcinoma; PegIFN, pegylated interferon; RBV, ribavirin; LC, liver cirrhosis; G-1, genotype 1; G-2/3, genotype 2 or 3; SVR, sustained virological response; RVR, rapid virological response; ETR, end-of-treatment virological response; ALT, alanine aminotransferase; AE, adverse event; SAE, severe adverse event; BMI, body mass index.

Introduction

Hepatitis C virus (HCV) infection frequently causes chronic liver disease leading to cirrhosis and hepatocellular carcinoma (HCC), and has become the main indication for liver transplantation worldwide and the leading cause of death among cirrhotic patients [1,2]. At least 20% of chronic hepatitis C (CHC) patients develops cirrhosis within 20 years [3]. Once cirrhosis is established, the annual risk of HCC, hepatic decompensation, and liver-related death is approximately 1–7%, 5%, and 2%, respectively [4–6]. Eradication and/or amelioration of HCV infection, therefore, have become a must in the clinical setting.

Numerous prospective and retrospective analyses have suggested that a sustained virological response (SVR), defined as HCV RNA levels of less than 50 IU/ml at the end of the 24-week follow-up after cessation of therapy, secondary to interferon (IFN)-based therapy, improves prognosis in terms of reduction of cirrhosis and HCC development and prolongation of survival [7–9]. Benefits are obtained mainly through the achievement of a successful viral eradication. In the past decade, combination

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therapy with pegylated interferon (PegIFN)-alpha plus ribavirin (RBV) has greatly improved the treatment efficacy and is the mainstream of treatment for CHC [2,6]. Current treatment recommendations derive from data collected in randomized registration trials [1,2]. However, these trials have usually been restrictive in their exclusion criteria and thus have not taken into account certain groups requiring a therapy such as patients with advanced liver disease or HCC [2]. At present, evidence regarding the efficacy of PegIFN/RBV therapy in these special groups of CHC patients is still scarce.

The aim of the current study was to assess and validate the efficacy and safety of PegIFN/RBV combination therapy by the current treatment guidelines in CHC patients with HCC after curative therapeutic strategies as compared to their cirrhosis counterparts. We also aimed to investigate the factors contributing to the treatment response to PegIFN/RBV combination therapy in this special population of HCV infected patients.

Methods

Selection of patients

Eligible patients were treatment-naive Taiwanese CHC patients, age >18 years, who (1) were seropositive for HCV antibodies and HCV RNA positive; (2) had undergone a liver biopsy within 6 months before entry, the result of which was consistent with chronic hepatitis; (3) displayed an increased serum alanine aminotransferase (ALT) level, defined as >1.5 times the upper limit of the normal range for at least two measurements within 6 months preceding the study entry. Other eligibility criteria included a neutrophil count >1500/mm^3, a platelet count >9 $\times$ 10^4/mm^3, a haemoglobin concentration >12 g/dl for men and 11 g/dl for women, a serum creatinine concentration <1.5 mg/dl, no pregnancy or lactation, and the use of a reliable method of contraception for women.

Patients with any of the followings were excluded from the study: active hepatitis A, hepatitis B surface antigen seropositive, HIV infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson's disease, α1-antitrypsin deficiency, history or other evidence of bleeding from esophageal varices or other conditions consistent with decompensated liver disease (Child–Pugh class B or C), overt hepatic failure, current alcohol misuse or history of alcohol misuse (>20 g/day for men and >10 g/day for women), history of a severe seizure disorder or current anticonvulsant use, a psychiatric condition, or previous liver transplantation.

HCC group

A total of 88 consecutive patients were recruited. Patients, presented with CHC concomitant with either HCC at very early (n = 10) or early (n = 78) stages, were classified according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Patients received curative treatment and/or interventions such as surgery, radiofrequency ablation (RFA), and pure ethanol injection (PEI) at least 3 months before entry. The treatment strategies were defined according to the BCLC stage-specific treatment approach and upon patient's consent after detailed explanation and discussion of the possible outcome by well-trained, board certified hepatologists. At entry, no evidence of HCC, either recurrent or *de novo*, was identified by imaging techniques such as abdominal ultrasonography, computerized tomography, magnetic resonance imaging, and angiography. Generalized health surveillance for malignancy from head to heel was performed to exclude the possibility of distant metastasis. Patients were excluded from the study if a decompensated state occurred before entry: Child–Pugh class $\geq$B, presence of ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, total bilirubin level >2 mg/dl, or serum albumin level <2.8 mg/dl.

Cirrhosis group

Ninety-one consecutive compensated cirrhotic treatment-naïve CHC patients served as controls. These patients had received a liver biopsy within 6 months before entry, the result of which was consistent with chronic hepatitis and cirrhosis. Moreover, before entry, no evidence of HCC was identified by imaging modalities, such as abdominal ultrasonography or computerized tomography during regular HCC surveillance. As for the HCC group, patients were excluded from the study if the decompensated state occurred before entry.

Study design

This study was an investigator-initiated study. This prospective, open-label, multi-center, case–control study was conducted from October 2006 through December 2009, in one medical center and two regional core hospitals in Taiwan. The ethical committee of the Kaohsiung Medical University Hospital approved the study before it began. A written informed consent for interviewing, anthropomorphic measurements, blood sampling, and medical record reviewing was obtained from patients prior to enrolment.

All enrolled patients received PegIFN α-2a (Pegasys, Hoffmann-La Roche, Basal, Switzerland) subcutaneously, at a dose of 180 μg/week, and oral RBV 1000–1200 mg/day in two divided doses for 24 or 48 weeks. Genotype-1 (G-1) and genotype-2 or 3 (G-2/3) patients received 48 and 24-week treatment, respectively. The dose of RBV was based on body weight (1000 mg RBV for weight <75 kg and 1200 mg RBV for weight >75 kg). All patients were monitored for further 24 weeks after the end of the treatment. End of follow-up was defined as the visit performed 24 weeks after the end of the treatment. Patients had biweekly outpatient visits during the first month and monthly visits during the rest of the treatment period and during the 24-week follow-up period. At each visit, they underwent a physical examination and adverse events were recorded. Treatment adherence was monitored via patient's treatment diaries and the return of used and unused pre-filled syringes and drug containers. The 80/80/80 adherence was defined as patients who had received >80% of expected PegIFN and RBV doses and completed at least 80% of the expected duration.

Safety assessments and dose modification

Adverse events (AE) were graded as mild, moderate, severe, or potentially life-threatening, according to a modified World Health Organization grading system. The dose of PegIFN was decreased by 50% and the dose of RBV lowered to 600 mg/day when severe adverse events (SAE) occurred or when laboratory results showed haemoglobin concentration <10 g/dl in patients with no cardiac disease, or haemoglobin decrease >2 g/dl in those with cardiac disease, white cell counts <3000/mm^3 or platelet counts <50,000/mm^3. Full doses could be resumed at the resolution of the event. If the event persisted, both drugs were discontinued. The treatment was permanently discontinued for life-threatening events or when laboratory results showed a haemoglobin concentration <7.5 g/dl in patients with no cardiac disease, haemoglobin concentration <12 g/dl in those with cardiac disease, after 4 weeks of dose reduction, white cell count <1500/mm^3, platelet count <30,000/mm^3, or serum creatinine concentration >2 mg/dl. Treatment discontinuation was defined by PegIFN treatment that was discontinued for >4 weeks. Patients had access to well-trained nursing staff at any time to ensure drug compliance. Subjects who experienced drug-associated AE were treated supportively and referred to specialists such as psychiatrists or ophthalmologists, if needed.

Efficacy assessments

The primary end point of this study was SVR assessment, which was defined as HCV RNA PCR-seronegative by the end of treatment and throughout the follow-up period. The others were classified as non-responders. Rapid virological response (RVR) was defined by PCR-negative serum HCV RNA at 4 weeks of treatment. End-of-treatment virological response (ETR) was defined as PCR-negative serum HCV RNA at the end of treatment. Relapse was defined as HCV RNA re-appearance during the follow-up period in patients who achieved an ETR. The primary end point measurement was based on an intention-to-treat analysis.

Laboratory analyses

Biochemical and hematological testing was performed by a central laboratory. Anti-HCV antibodies were detected using a third-generation, commercially available enzyme-linked immunosorbent assay kit (AxSYM 3.0, Abbott Laboratories, Chicago, IL). Detection of serum HCV RNA was performed using a standardized automated qualitative reverse transcription PCR assay (COBAS AMPLICOR Hepatitis C Virus Test, ver. 2.0, Roche, Branchburg, NJ; detection limit 50 IU/ml). Quantitative serum HCV RNA levels were measured using the branched DNA assay (Versant HCV RNA 3.0, Bayer, Tarrytown, NJ; quantification limit 615 IU/ml). High