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Clinical and Virological Responses to Clevudine Therapy of Hepatocelluar Carcinoma Patients with Chronic Hepatitis B

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Background/Aims: The clinical effects of clevudine have been reported in patients with chronic hepatitis B virus infections (CHIs). In this investigation, we assessed whether clevudine induced biochemical and virological improvements in hepatocellular carcinoma (HCC) patients with CHI. **Methods:** Fifty-four patients who received 30 mg clevudine for more than 24 weeks between 2007 and 2009 at the National Cancer Center Hospital, Korea, were enrolled. Among these cases, 39 had HCC (CHI/HCC group) and 15 did not (CHI group). **Results:** In relation to the CHI group, the CHI/HCC group was older (55.5 years.) and had a higher liver cirrhosis rate (79.5%) ($p<0.05$). Median changes in serum hepatitis B virus (HBV) DNA levels from baseline at weeks 12, 24, and 36 of treatment in the CHI/HCC group were not significantly different from those of the CHI group (-2.3, -2.7, -2.6 vs -1.7, -1.8, -2.4, respectively). HBV DNA <2,000 copies/mL was achieved in 76.5% of the CHI/HCC group at 24 weeks. Rates of ALT normalization in the CHI/HCC and CHI groups were 62.5% and 66.7%, respectively ($p>0.05$). Liver function was preserved with clevudine treatment in patients displaying response or stable disease under anti-cancer therapy. Four patients (7.4%) developed viral resistance during clevudine therapy. Among these, one was naïve, and three had previously received antiviral therapy. One CHI/HCC patient (1.9%) discontinued clevudine treatment due to symptomatic myopathy. **Conclusions:** Our findings clearly indicate that clevudine has comparable antiviral and biochemical effects in patients with CHI and with CHI/HCC and preserves the underlying liver function in HBV-related HCC patients. **(Gut Liver 2011;5:82-87)**

Key Words: Chronic hepatitis B virus infection; Hepatocellular carcinoma; Clevudine

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer worldwide, and the third largest cause of cancer-related mortality.[1] Treatment strategies of HCC are dependent on both the underlying liver disease status and tumor stage. Poor liver function of HCC patients hinders curative treatment, even through the early stages of tumor.

In Asian countries, including Korea, 70–80% of patients with HCC have chronic hepatitis B virus (HBV) infection,[2,3] and the underlying chronic hepatitis B status affects the decision for treatment strategies. Therefore, treatment of chronic hepatitis B and control of underlying liver function are as important as treating the tumors themselves.[4]

Systemic chemotherapy,[5] radiation therapy[6] and surgical resection[7] of patients with HBV-related HCC are complicated by HBV re-activation and chronic hepatitis B exacerbation. In addition, high HBV load prior to chemotherapy has an adverse effect on the survival of HCC patients with chronic HBV infection (CHI).[8] These findings suggest that incorporation of antiviral therapies to reduce the HBV viral load should be considered in the management of HBV-related HCC. Antiviral treatment may render HBV-related HCC patients more tolerant of HCC therapy, ultimately leading to better prognosis. A previous study by our group showed for the first time that lamivudine has comparable antiviral effects in patients with CHI and CHI/HCC and improves underlying liver function in the latter group.[4]

Clevudine (1-[2-deoxy-2-fluoro-_-L-arabinofuranosyl] thymine, L-FMAU), a pyrimidine analog with potent and sustained antiviral activity against HBV,[9,10] was approved for prescription in 2007 in South Korea. A unique advantageous characteristic of clevudine is prolonged suppression of viral replication even after withdrawal of treatment, which has been demonstrated both *in vitro* and *in vivo*.[9,11-13] Clinical effects of clevudine have been reported in patients with HBeAg-positive or -negative

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chronic hepatitis B. However, current knowledge on the effects of clevudine is insufficient, and the influence of this drug in HBV-related cirrhosis or HCC patients remains to be established. In this investigation, we therefore assessed whether clevudine induces biochemical and virological improvements in HCC patients with CHI.

MATERIALS AND METHODS

1. Patients

This study is a retrospective evaluation of 54 CHI patients receiving 30 mg clevudine (Levovir®; Buckwang Pharmaceutical Co., Seoul, Korea) once a day for at least 6 months from August 2007 to February 2009 at the National Cancer Center Hospital (Goyang, Korea). Among the patients, 39 had chronic hepatitis B infection and HCC (CHI/HCC group), and 15 had CHI without HCC (CHI group). Patients with other viral infections, including hepatitis C, D, and human immunodeficiency virus, were excluded. All patients from both groups contained serum HBV DNA $>10^5$ copies/mL, as assessed using the branched DNA method. Moreover, all patients displayed serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels greater than twice the upper normal limit or signs of hepatic decompensation, including hyperbilirubinemia, prolonged prothrombin time and ascites. Diagnosis and treatment of HCC was based on the guidelines of the Korean Liver Cancer Study Group and the National Cancer Center, Korea.[14] Written informed consent was obtained from all patients participating in this study, and the Institutional Review Boards approved the study.

2. Methods

All patients underwent baseline examinations, including liver function tests (ALT, AST, total bilirubin, albumin and protein), evaluation of creatinine level, prothrombin time, common blood counts (white cell, hemoglobin, and platelet counts), and HBV viral analyses, including serum HBV DNA quantification, detection of hepatitis B surface antigen, anti-HBs, hepatitis B e antigen (HBeAg) and anti-HBe. Liver function tests were performed every 2-3 months. Serum HBV DNA and HBeAg/anti-HBe levels were monitored every 3-6 months. Serum HBV DNA was measured using the bDNA method (Versant HBV DNA 3.0; Bayer Healthcare LLC, NY, USA; lower limit of detection=2×10^3 copies/mL). Viral breakthrough was defined as the reappearance of serum HBV DNA to a detectable level with the hybridization assay or $>10^5$ copies/mL using the bDNA assay during clevudine therapy. Genotypic mutations were detected by restriction fragment mass polymorphism analysis in cases of viral breakthrough. Tumor characteristics, including size, number, type, vascular invasion and modified Union Internationale Contre le Cancer (UICC) stage, were evaluated using spiral contrast-enhanced computerized tomography (CT) or dynamic magnetic resonance imaging (MRI). Patients in the CHI/HCC group under-

Table 1. Patient Characteristics at Baseline

	CHI/HCC group (n=39)	CHI group (n=15)	Total (n=54)	p-value
Gender				0.478*
Male, n (%)	31 (79.5)	10 (66.7)	41 (75.9)	
Female, n (%)	8 (20.5)	5 (33.3)	13 (24.1)	
Median age, yr	55.5	43.5	52.6	0.044†
Liver cirrhosis, n (%)	31 (79.5)	4 (26.7)	35 (64.8)	0.001*
Positive HBeAg, n (%)	14 (35.9)	8 (53.3)	22 (40.7)	0.355*
Median Serum HBV DNA, $\log_{10}$ copies/mL	6.6	6.3	6.4	0.434†
Median ALT, U/L	45.0	68.0	52.5	0.137†
Mean ALT, U/L	87.0	98.3	90.2	0.755‡
ALT				0.959§
<2X ULN at baseline, n (%)	27 (69.2)	10 (66.7)	37 (68.5)	
2X to <5X ULN at baseline, n (%)	9 (23.1)	4 (26.7)	13 (24.1)	
≥5X ULN at baseline, n (%)	3 (7.7)	1 (6.7)	4 (7.4)	
Median platelets, $\times10^3/mm^3$	119	194	137	<0.001
Median total bilirubin, mg/dL	0.9	0.6	0.8	0.031
Median albumin, g/dL	3.8	4.3	4	<0.001
Prior antiviral treatment, n (%)	2 (5.1)	5 (33.3)	7 (13.0)	0.014*
Median treatment duration, wk	34.9	39.0	37.6	0.192†

CHI, chronic hepatitis B virus infection; HCC, hepatocellular carcinoma; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase.
*Two-sided Fisher's exact test; †Mann-Whitney U test; ‡t-test; §Chi-squared test.

went imaging tests (CT, MRI, or sonography) every 1-3 months, while those in the CHI group were subjected to tests every 4-6 months. Changes in underlying liver function were evaluated using Child-Pugh scores. Clinical diagnosis of cirrhosis was based on the presence of stigmata of portal hypertension, as evident from splenomegaly with thrombocytopenia, ascites or varices, demonstrated endoscopically or radiologically.[15]

3. Statistical analysis

All data were analyzed using the STATA 9.0 software program (StataCorp, College Station, TX, USA). Continuous variables were expressed as means±standard deviations (SDs). Differences between the CHI/HCC and CHI groups were evaluated using Student's t-test or Fisher's exact test, as required. Changes in the underlying liver function in the CHI/HCC group were assessed using paired t-test and Wilcoxon's signed-rank test. Results were considered statistically significant at $p<0.05$, and not significant (NS) otherwise.

RESULTS

1. Baseline characteristics

The mean±SD duration of clevudine therapy was 37±12 weeks in the CHI/HCC group and 48±24 weeks in the CHI group (p=0.095). Baseline AST/ALT levels did not differ significantly between the two groups (87±12 IU/mL vs 98±104 IU/mL, p=0.734). On average, the CHI/HCC group was older (55.5 years), with a higher liver cirrhosis rate (79.5%), higher bilirubin level (0.9 mg/dL), lower platelet count (119K) and lower albumin level (3.8 g/dL) ($p<0.05$) than the CHI group (Table 1).

Baseline tumor characteristics, initial treatment modality and survival of the CHI/HCC group are listed in Table 2. According to the modified UICC staging system of HCC, 4, 11, 17, 5, and 2 patients were classified as stages I, II, III, IVa, and IVb, respectively. The initial therapeutic modalities were as follows: surgery (9 patients), radiofrequency ablation (1 patient), transarterial chemo-embolization (25 patients), chemotherapy (5 patients), and best supportive care (1 patient). Median follow-up duration from HCC diagnosis was 55.1 weeks.

2. Effect of clevudine on hepatitis B viral status in chronic hepatitis B and hepatocellular carcinoma

Median changes in serum HBV DNA levels (log_{10} copies/mL) from baseline at weeks 12, 24, and 36 of treatment in the CHI/HCC group were not significantly different from those in the

Table 2. Baseline Tumor Characteristics and Clinical Courses in the Chronic Hepatitis B Virus Infection/Hepatocellular Carcinoma Group (n=39)

Tumor characteristic	Value
Tumor size (<2/2-5/5-10/≥10 cm)	6/15/17/1
Tumor no. (1/2/3-4/≥5)	26/5/5/3
Tumor type (well-defined/ill-defined)	23/16
Portal vein invasion (yes/no)	14/25
Modified UICC stage (I/II/III/IVa/IVb)	4/11/17/5/2
Initial treatment (surgery/RFA/TACE/chemotherapy/BSC)	9/1/25/3/1
Child-Pugh class A/B/C	37/2/0
No. of survivors (yes/no)	33/6
Median follow-up duration from diagnosis, wk	55.1

Data are presented as number.
UICC, Union Internationale Contre le Cancer; RFA, radiofrequency ablation; TACE, transarterial chemo-embolization; BSC, best supportive care.

Table 3. Serum HBV DNA Response and Adverse Events of Clevudine Therapy

	HCC (n=39)	No HCC (n=15)	p-value
Median log_{10} HBV DNA at baseline	6.6	6.3	0.434*
Median change in HBV DNA, log_{10} copies/mL			
From baseline to week 12	-2.3	-1.7	0.579*
From baseline to week 24	-2.7	-1.8	0.204*
From baseline to week 36	-2.6	-2.4	0.657*
HBV DNA ≤2,000 copies/mL			
Week 12, n/N (%)	20/30 (66.7)	6/14 (42.9)	0.135†
Week 24, n/N (%)	26/34 (76.5)	6/14 (42.9)	0.025†
Week 36, n/N (%)	12/15 (80.0)	4/10 (40.0)	0.041†
Viral resistance, n (%)	2 (5.1)	2 (13.3)	0.306‡
High serum creatinine level (>1.4 mg/dL)	3 (7.7)§	0	0.552‡
Myopathy	1 (2.5)	0	1‡

HBV, hepatitis B virus; HCC, hepatocellular carcinoma.
*Mann-Whitney U test; †Chi-squared test; ‡Two-sided Fisher's exact test; §Two were Child-Pugh class C cirrhotic patients and 1 had rupture of HCC.

CHI group (-2.3, -2.7, -2.6 vs -1.7, -1.8, -2.4, respectively) (Table 3). HBV DNA <2,000 copies/mL was achieved in 76.5% of patients at 24 weeks in the CHI/HCC group. One patient (7.1%) of the CHI/HCC group displayed HBe antigen seroconversion during clevudine treatment.

Four patients (7.4%), including one naïve and three previously exposed to antiviral therapy (2 lamivudine and 1 clevudine phase III study), developed viral resistance during clevudine therapy (CHB/HCC 5.1% vs CHB 13.3%, p=0.306). Viral resistance developed after 36, 39, 50, and 74 weeks of clevudine treatment, respectively. Analysis of HBV DNA polymerase by direct sequencing revealed the presence of the M204I mutation in all 4 patients. Among the patients analyzed in this study, 47 were naïve and 7 had a history of prior antiviral therapy. The resistance rate of patients exposed to prior antiviral therapy was significantly higher than that of naïve patients (42.9% vs 2.1%, p=0.005).

3. Effect of clevudine on underlying liver function in chronic hepatitis B virus infection and hepatocellular carcinoma patients

Comparison of clinical outcomes in the two patient groups revealed that after 6 months of clevudine therapy, the rates of ALT normalization in the CHI/HCC and CHI groups were statistically similar (62.5% [15/24] and 66.7% [6/9], respectively [p>0.05]). Despite clevudine treatment, the mean Child-Pugh score was significantly increased in 11 patients with progressive disease (from 5.3±0.5 to 7.7±2.6, p=0.011). However, liver function was preserved upon clevudine treatment in 28 patients displaying response or stable disease under anti-cancer therapy, including 10 cases of surgical resection, 1 radiofrequency ablation, and 17 transarterial chemoembolization and/or radiation therapy cases (from 5.5±1.0 to 5.5±1.1, p=1.000).

Serum creatinine levels were increased in 3 CHI/HCC patients during clevudine therapy (Table 3). Two of these patients were classified as Child-Pugh class C in terms of liver function due to HCC progression, and 1 had rupture of HCC. One (1.9%) CHI/HCC patient who was subjected to surgical resection discontinued clevudine treatment due to symptomatic myopathy. Walking disturbance developed after 80 weeks of clevudine treatment. The myopathy symptoms of the patient subsequently improved after clevudine withdrawal, and no residual sequelae remained after 3 months.

DISCUSSION

One of the primary difficulties in treating HCC is that, in over 85% of cases, this cancer type develops in the cirrhotic liver.[2,16] Many chronic hepatitis B cases progress to liver cirrhosis, which is the strongest underlying risk factor for HCC, and prevalent in more than 70% of Asian HCC patients.[17,18] Treatment strategies for HBV-related HCC, including surgical resection, radiation therapy and systemic chemotherapy, could result in HBV reactivation and exacerbation of hepatitis.[5-8] In a previous report by our group,[4] lamivudine therapy effectively improved the underlying liver function, allowing more aggressive treatment of HCC in CHI patients. Clevudine has been employed in South Korea since 2007, but the efficacy of clevudine therapy on HBV viral status and underlying liver function in HBV-related HCC is not yet to be established. Data from the present study demonstrate the usefulness of clevudine therapy in patients with HBV-related HCC. Liver function was preserved with clevudine treatment in HCC patients showing no disease progression under anti-cancer therapy. Therefore, clevudine therapy may also be considered for the prevention of liver function deterioration during and after anti-cancer therapy in HBV-related HCC.

During 24 weeks of clevudine therapy, the rates of ALT normalization were 68.2% in patients with HBeAg-positive chronic hepatitis B[12] and 74.6% in patients with HBeAg-negative chronic hepatitis B.[13] Our data showed slightly lower rates of ALT normalization, specifically, 62.5% and 66.7% in the CHB/HCC and CHB groups, respectively. In our study, 15 patients of the CHI/HCC group and 6 patients of the CHI group displayed normal ALT levels in a baseline study and they were excluded in the analysis of ALT normalization. No significant differences in HBe antigen positivity were evident between the two groups (35.9% vs 53.3%) (Table 1).

While the CHI/HCC group included more liver cirrhosis patients (79.5% vs 26.7%), we observed no significant differences in ALT normalization and serum DNA reduction between the two groups. The results suggest compatible efficacy of clevudine in HBV cirrhosis patients. Further large-scale studies on clevudine safety and efficacy in HBV-positive liver cirrhosis patients are ongoing in South Korea.

Previous studies reported median serum HBV DNA reduction from baseline at week 24 of 5.10 $\log_{10}$ copies/mL in patients with HBeAg-positive CHB and 4.25 $\log_{10}$ copies/mL in patients with HBeAg-negative CHB.[12,13] In our study, median changes in serum HBV DNA levels at 24 weeks in the CHB/HCC and CHB groups were -2.7 and -1.8 $\log_{10}$ copies/mL, respectively. This relatively small reduction in serum HBV DNA levels may be due to reduced baseline DNA levels and higher rates of lower baseline ALT levels in our study population (Tables 1, 2), compared with those reported previously; 6.6-6.3 vs 8.29-6.92 $\log_{10}$ copies/mL, 68.5% vs 31.8-26.4% ALT <2X ULN at baseline, respectively.[12,13] Owing to low efficacy, antiviral treatment is not generally recommended to HBV-positive patients with serum HBV DNA levels >20,000 IU/mL and normal or minimally elevated ALT.[19] Careful consideration of the patient age, severity of liver disease, likelihood of response, and potential adverse events is essential prior to initiation of treatment. In our study, patients in the CHI/HCC group needed antiviral therapy for prevention and treatment of chronic hepatitis B exacerbation during anticancer therapy, and most patients in the CHI group displayed

fluctuating ALT history and coarseness in liver ultrasonography.

We observed viral resistance in 4 patients (7.4%) during clevudine therapy. Among these, one was naive and three were previously subjected to antiviral therapy (lamivudine or clevudine). The resistance rate of patients with prior antiviral therapy was significantly higher than that of naïve patients (42.9% vs 2.1%, p=0.005). Knowledge of clevudine resistance is insufficient at present. Phase III clevudine studies revealed no resistance development during a 24-week therapy course in HBeAg-positive and -negative chronic hepatitis B.[12,13] Genotypic analysis at the end of 24 weeks disclosed rtA181A/T, rtA181T, and rtV191V/I substitutions, but no associations with viral breakthrough.[12] Recently, development of clevudine resistance during therapy in a patient who received prior lamivudine therapy was reported.[20-22] Similar to our findings, the most frequent mutation was identified as M204I. A further binding mode study reveals a steric clash in the case of M204I HBV due to the unfavorable position and orientation of a methyl group of I204. This may attribute to the several-fold reduced susceptibility of clevudine in M204I and the dual mutant, L180M/M204I.[23] A detailed history of previous antiviral therapy is required before introducing clevudine treatment. We enrolled a higher number of patients with prior antiviral treatment in the CHI group, compared with the CHI/HCC group (p=0.014). The lower HBV negativity <2,000 copies/mL (42.9%) at 24 weeks of treatment may be due to this patient population profile (Table 3).

To date, the results of five clinical trials on clevudine therapy have been published, including phase II studies showing no serious adverse events, including myopathy, after 24 weeks of treatment.[9,12,13,24,25] However, several hepatitis B patients develop myopathy during long-term clevudine therapy.[26,27] Moreover, long-term clevudine therapy induces depletion of mitochondrial DNA and leads to mitochondrial myopathy associated with myonecrosis.[26] In our study, one CHI/HCC (1.9%) patient discontinued clevudine treatment due to symptomatic myopathy. His clinical symptoms subsequently improved after clevudine withdrawal, and no residual symptoms remained. While the number of myopathy cases was low and severity was mild, further investigations are needed to clarify the safety of long-term clevudine therapy.

Our study has several limitations. Study limitation included a small sample size and relatively short-term follow-up duration. In addition, HBV DNA was measured using the bDNA method in this study. The real-time quantitative PCR assay is more sensitive than the bDNA method. The use of less sensitive method of HBV DNA quantification could have an influence on the analysis of virologic response or breakthrough. A large prospective study with long-term follow-up is warranted to determine the efficacy of clevudine therapy in CHI/HCC group.

In conclusion, we show that clevudine exerts comparable antiviral and biochemical effects in patients with CHI and CHI/HCC and preserves the underlying liver function in HBV-related HCC. Thus, clevudine may facilitate more aggressive treatment in HCC patients with CHI.

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