Prevention by Lamivudine of Hepatocellular Carcinoma in Patients Infected with Hepatitis B Virus

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Background/Aims: This study evaluated the prevention by lamivudine of hepatocellular carcinoma (HCC) in chronic hepatitis B patients. **Methods:** Lamivudine therapy was administered to 879 of the 2,511 patients who satisfied our analysis inclusion criteria. A Cox regression model revealed that four factors increased the prevalence of HCC: gender (females; OR=0.53, $p=0.006$), age (≥ 40 years; OR=4.64, $p<0.001$), platelet count ($\geq 100 \times 10^3/\text{mm}^3$; OR=0.35, $p<0.001$), and alcohol consumption (≥ 80 g/day; OR=1.79, $p=0.004$). Five hundred and eighty-nine patients in the lamivudine-treated group and 589 patients in the control group were selected for a matched case-control study. The mean follow-up periods were 2.8 and 5.1 years in the lamivudine-treated and control groups, respectively. **Results:** HCC occurred in 10 patients (1.7%) of the lamivudine group, with an incidence rate of 0.61% patients/year, and in 65 patients (11.0%) of the control group, with an incidence rate of 2.16% patients/year. The cumulative incidence of HCC was lower in the lamivudine group than in the control group ($p=0.0117$, log-rank test). **Conclusions:** Lamivudine can reduce the incidence of HCC in patients suffering from chronic hepatitis B. (*Gut and Liver* 2007;1:151-158)

Key Words: Lamivudine; Chronic hepatitis B; Hepatocellular carcinoma; Prevention

INTRODUCTION

More than 350 million persons in the world are infected with chronic hepatitis B virus (HBV).¹ Korea is known to be one of the endemic areas in the world for HBV infection; For Koreans, the infection is usually acquired per-

inatally or in early childhood, and the seropositivities for HBs antigen are 5.1% in males and 4.1% in females.² The number of HBV carriers is decreasing as a result of preventing mother-child transmission through the use of HBV vaccines and hepatitis B immunoglobulin (HBIG).^{2,3} However, many persons born before the 1980s still suffer from HBV-related chronic liver disease and hepatocellular carcinoma.

Chronic HBV infection is the most common cause of HCC worldwide. The annual incidence of HCC in European patients with chronic hepatitis B is about 2.2% for patients with compensated cirrhosis, and the five-year cumulative incidence is about 10%. The incidence of HCC for Asians is higher with an annual rate of 3.2% in patients with cirrhosis and the five-year cumulative incidence is 15%.^{4,5}

Although the exact mechanisms by which HBV causes HCC are unclear, there is strong association between the serum level of HBV DNA and hepatocellular carcinoma.⁶ Two pathways have been proposed. One involves the chronic necroinflammation of hepatocytes, cellular injury, mitosis and hepatocyte regeneration. The other pathway involves the direct carcinogenicity of HBV through chromosomal integration. It is likely that both pathways contribute to HBV-related hepatic carcinogenesis,⁷⁻⁹ and it can be speculated that elimination or suppression of HBV will reduce the risk of HCC.^{9,10}

Lamivudine is the first nucleoside analogue licensed for the treatment of chronic HBV. Lamivudine can be taken orally in a dosage of 100 mg daily. It is generally well tolerable and it has an excellent safety profile.⁵ It suppresses HBV DNA replication, improves the liver function and liver histology and increases HBe antigen loss/seroconver-

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sion.¹¹⁻¹⁷ It can be contemplated that lamivudine might reduce the incidence of HCC. However, evidences regarding the effect of lamivudine on occurrence of HCC are lacking. Therefore, we evaluated the effects of lamivudine on preventing HCC and estimated the power of this prevention effect.

MATERIALS AND METHODS

1. Study design

We reviewed the medical records of the patients who were diagnosed as HBV-related liver disease at Yeungnam University hospital from Jan 1983 to Dec 2005. The patients without HCC on their first visit and whose follow-up period was over one year were recruited. The follow-up period was defined as the first prescription day to the last prescription day in the lamivudine-treated group and from the first-visit day to the last-visit day in the lamivudine-untreated group. The primary endpoint of the study was occurrence of HCC in both groups. In addition, in cases of lamivudine untreated group, another endpoint would be initiating lamivudine treatment.

The patients were excluded from the study if they 1) have co-infected hepatitis C virus (HCV) 2) have other uncontrolled malignancies detected upon the first visit 3) were diagnosed as having HCC within the one year after the enrollment 4) have combined serious medical disease such as rheumatic disease, chronic obstructive lung disease, or severe cardiopulmonary disease.

All the patients had their medical records reviewed re-

garding age, gender, the family history, alcohol history, any interferon treatment history and existing ascites. The result of 1 laboratory tests (AST, ALT, total bilirubin, platelet, albumin, HBeAg, HBeAb and HBV DNA titer) upon enrollment were evaluated.

A positive family history for HBV was suspected if more than one of the patient's first-degree relative had HBV infection. Significant alcohol consumption was defined as alcohol consumption of 20 g or more per day during the follow-up. Those patients had the amount of consumed alcohol recorded.

2. Patients

This study included 8,014 patients who had chronic hepatitis B infection without HCC detected upon their first visit. Among them, 1,867 patients had received lamivudine therapy at least once and 6,147 patients had not. Among the lamivudine-treated group (100 mg/day), 879 patients were followed for over one year and satisfied our inclusion criteria for analysis. Among the lamivudine-untreated group, 1,632 patients were followed for over one year (Fig. 1, 2).

3. Control study

For conducting a matched case-controlled study, we selected 4 HCC-related factors (gender, age, the platelet count and the alcohol history) for the Cox regression model analysis. We also included 2 more factors associated with liver cirrhosis: serum albumin and existence of ascites. The age variable was divided into three groups

Fig. 1. Schematic flow chart for patient enrollment. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LAM, lamivudine, F/U, follow-up period; HCV, hepatitis C virus; COPD, chronic obstructive pulmonary disease.

Fig. 2. Yearly distribution of enrolled patients according to lamivudine-treatment or not. Lamivudine has been available since 1997 in our hospital.

since it is known to be an independent risk factor for the development of HCC. The platelet count was categorized into three groups because it is closely related to liver fibrosis. The enrolled patients were classified into 144 categories by these 6 factors for the case-controlled study: gender (male and female), age (≤ 39 , 40-49 and ≥ 50 years), platelet count (≤ 99 , 100-149 and $\geq 150 \times 10^3/\text{mm}^3$), serum albumin (< 3.5 and ≥ 3.5 g/dL), alcohol consumption (< 20 and ≥ 20 g/day) and ascites (yes or no). Five hundred eighty nine patients in the lamivudine-treated group and 589 patients in the lamivudine-untreated group were selected respectively by using the SPSS program.

4. Statistical analysis

We used SPSS program (Version 11.5, Chicago, USA) for the analysis. The variables in two groups were compared by Student's t-test (numerical data) or chi-square test (categorical data), and differences were regarded as significant for p values < 0.05 on both sides. The cumulative incidence of HCC was analyzed by the Kaplan-Meier method and this value was compared between the two groups by the log-rank test. Differences were regarded as significant for p values < 0.05 on both sides. The cumulative incidence of HCC was reported as an annual incidence rate (%/patients/year).

RESULTS

1. Baseline clinical characteristics

Table 1 reveals the comparison of baseline clinical characteristics between the lamivudine-treated group and the lamivudine-untreated group. Significant differences were found in age, the family history, the alcohol history, the amount of alcohol consumed, ascites, the levels of AST

Table 1. Baseline Clinical Characteristics of the Lamivudine-Treated and Lamivudine-untreated Patients

	Lamivudine-treated group (n=879)	Lamivudine-untreated group (n=1,632)	p-values
Clinical data			
Age (yrs)	40.2 $\pm$ 12.3	38.1 $\pm$ 13.4	< 0.001
Gender (M/F), n (%)	613/266 (69.7/30.3)	1167/465 (71.5/28.5)	NS*
Family history, yes (%)	465 (52.9)	703 (43.1)	0.001*
Alcohol (≥ 20 g/day), n (%)	199 (22.6)	444 (27.2)	0.005*
Alcohol consumption (g/day)	17 $\pm$ 41	25 $\pm$ 51	< 0.001
Interferon history, yes (%)	98 (11.2)	148 (9.1)	NS*
Ascites, yes (%)	50 (56.9)	161 (9.9)	0.001*
Laboratory data			
AST (IU/L)	126 $\pm$ 160	88 $\pm$ 130	< 0.001
ALT (IU/L)	162 $\pm$ 184	105 $\pm$ 171	< 0.001
Total bilirubin (mg/dL)	1.2 $\pm$ 1.5	1.1 $\pm$ 0.9	NS
Albumin (g/dL)	4.0 $\pm$ 0.6	4.1 $\pm$ 0.6	NS
Platelet ($\times 10^3/\text{mm}^3$)	161 $\pm$ 70	181 $\pm$ 79	0.001
Child-Pugh classification			
NC/A/B/C: n (%)	465/313/77/24 (52.9/35.6/8.8/2.7)	1051/346/186/49 (64.4/21.2/12.0/3.1)	NS*
Virological data			
HBe Ag, positive (%)	696 (79.4)	769 (51.2)	< 0.001 *
HBV DNA (pg/mL)	1,297.8 $\pm$ 2,441.5	622.4 $\pm$ 3,589.3	< 0.001
Follow-up period (yrs)	2.9 $\pm$ 1.6	5.3 $\pm$ 4.2	

NC, non-cirrhosis; Values: mean $\pm$ standard deviation.

*Statistical analysis: Student t-test or chi-square test.

and ALT, the platelet count, the level of HBeAg and the duration of follow-up. HCC occurred in 17 of the 879 patients (1.9%) in the lamivudine-treated group and in 157 patients of the 1632 patients (9.6%) in the lamivudine-untreated group. The mean follow-up periods were 2.9 and 5.3 years, respectively. Thus, the crude incidences of HCC were 0.66% and 1.81% (patients/year) in the lamivudine and control groups, respectively (Table 1).

2. HCC-related factors using the Cox regression model

The factors related to HCC were analyzed using the Cox regression model (Table 2). The following variables were selected by the forward stepwise selection method: gender (female, OR=0.53, p=0.006), age (≥ 40 years,

Table 2. Estimation of the Hepatocellular Carcinoma-Related Risk Factors by the Cox Regression Model

	Odds ratio	95% Confidence interval (CI)	p-value
Gender			
Male	1		
Female	0.53	0.33-0.84	0.006
Age			
<40 years	1		
≥40 years	4.64	3.01-7.14	<0.001
Platelet ($\times 10^3/\text{mm}^3$)			
<100	1		
≥100	0.35	0.24-0.52	<0.001
Alcohol (g/day)			
<80	1		
≥80	1.79	1.20-2.66	0.004
Albumin (g/dL)			
<3.0	1		
≥3.0	0.87	0.49-1.52	0.613
Ascites			
No	1		
Yes	1.15	1.20-2.66	0.632
Lamivudine treatment			
No	1		
Yes	0.25	0.15-0.40	0.014

OR=4.64, $p<0.001$), platelet count ($\geq 100 \times 10^3/\text{mm}^3$, OR=0.36, $p<0.001$), alcohol consumption (≥ 80 g/day, OR=1.79, $p=0.004$) and lamivudine therapy (yes, OR=0.25, $p=0.014$).

3. Six-factor matched case-controlled study

The comparison of factors between the lamivudine group and a control group is summarized in Table 3. The two groups were not different in terms of alcohol history (20 g/day cut-off), although the amount of alcohol consumed in the control group was higher (mean: 23 vs 18 g/day, respectively, $p=0.018$). Also, significant differences between two groups were noted for the level of AST, ALT and level of HBV DNA, and HBe antigen positivity. The other variables were not statistically different.

The mean follow-up period was 2.8 years in the lamivudine group and 5.1 years in the control group. HCC occurred in 10 patients in the lamivudine group and 65 patients in the control group. Thus, the annual incidence of HCC is 0.61%/(patient/year) and 2.16%/(patient/year), respectively. According to the Kaplan-Meier analysis and log-rank test, the cumulative incidence of HCC in the lamivudine group was significantly lower than that in the control group ($p=0.0117$, log-rank; Fig. 3).

Table 3. Comparison of Background Factors between the Lamivudine Group and the Control group at First Visit (A Six-Factor Matched Case-Controlled Study)

	Lamivudine group (n=589)	Control group (n=589)	p-values
Clinical data			
Age (years)	39.5±12.7	39.5±13.5	NS
Gender (M/F), n (%)	415/174 (70.5/29.5)	415/174 (70.5/29.5)	NS
Family history, yes (%)	309 (52.4)	290 (49.2)	NS
Alcohol (≥ 20 g/day), n (%)	186 (31.6)	186 (31.6)	NS
Alcohol consumption (g/day)	18±43	24±50	0.018
Interferon history, yes (%)	64 (10.9)	48 (8.1)	NS
Ascites, yes (%)	26 (4.4)	26 (4.4)	NS
Laboratory data			
AST (IU/L)	125±153	78±101	<0.001
ALT (IU/L)	158±174	86±122	0.001
Total bilirubin (mg/dL)	1.2±1.6	1.1±0.8	NS
Albumin (g/dL)	4.0±0.6	4.1±0.6	NS
Platelet ($\times 10^3/\text{mm}^3$)	166±72	173±77	NS
Child-Pugh classification			
NC/A/B/C, n (%)	336/188/45/20 (57.1/31.9/7.6/3.4)	333/195/50/11 (56.5/33.1/8.5/1.9)	NS
Virological data			
HBe Ag, positive (%)	475 (80.6)	262 (44.5)	<0.001*
HBV DNA (pg/mL)	1,350.9±2,466.0	614.9±4,471.4	0.001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; NC, non-cirrhosis; HBe Ag, Hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NS, statistically non-significant ($p>0.05$).

Values: mean±standard deviation.

*Statistical analysis: Student t-test or chi-square test.

4. Comparing factors between the HCC-developed and the HCC-undeveloped group

Table 4 demonstrates the comparison of the factors between the HCC-developed and HCC-undeveloped group among the lamivudine-treated patients.

In the HCC-developed group among patients who received lamivudine therapy, the age was older ($p=0.009$), the amount of alcohol consumed was greater ($p=0.005$), and the serum albumin level and platelet count were lower ($p=0.005$ and 0.014 , respectively). Similar to the lamivudine-treated group, we found significant differences in these factors among the lamivudine-untreated group between HCC-developed and HCC undeveloped patients

Fig. 3. Comparison of the cumulative incidence of HCC between the lamivudine group and the control group.

Table 4. Annual Incidences of Hepatocellular Carcinoma in the Lamivudine Group and in the Control Group

	Lamivudine group (n=589)	Control group (n=589)	p-values
Follow-up period (years)	2.8±1.6	5.1±3.9	NS
age at diagnosis	51.6±7.2	50.8±12.0	
HCC, n (%)			
annual incidence	10 (1.7)	65 (11.0)	<0.001*
(%/patient/year)	0.61	2.16	

NS, statistically non-significant ($p > 0.05$).

* $p < 0.05$.

(Table 5).

DISCUSSION

The aims of the present study are to determine whether lamivudine can help preventing HCC in chronic hepatitis B patients. There is no doubt that this study has a few limitations: this is not a prospective study, this does not include information during follow-up, the follow-up duration is short, this does not consider the effect of emergence of viral resistance during lamivudine therapy and this does not evaluated liver histology and possible confounding effect of other drugs.

Despite these limitations, we believe that this study is well-designed with having relevant control group. Although a prospective randomized double-blind study is needed as a properly matched case-control study, conducting a randomized double-blind study for a drug with proven benefit is difficult due to ethical problems. In our hospital, lamivudine has been available since 1997. Therefore, the patients with chronic hepatitis B detected

Table 5. Comparison of Background Factors between Patients Who Developed Hepatocellular Carcinoma and Those Who did not in the Lamivudine Group

	Patients with HCC (n=17)	Patients without HCC (n=862)	P-values
Clinical data			
Age (years)	47.9±7.2	40.0±12.3	0.009
Gender (M/F), n (%)	13/4 (76.5/23.5)	600/262 (69.6/30.4)	NS
Family history, yes (%)	5 (29.4)	460 (53.4)	0.071*
Alcohol (≥ 20 g/day), n (%)	5 (25.0)	194 (22.5)	NS
Alcohol consumption (g/day)	50.9±87.3	15.9±39.6	0.005
Interferon history, yes (%)	1 (5.9)	97 (11.3)	NS
Ascites, yes (%)	1 (5.9)	49 (5.7)	NS
Laboratory data			
AST (IU/L)	111±114	127±161	NS
ALT (IU/L)	121±200	162±184	NS
Total bilirubin (mg/dL)	1.2±0.4	1.2±1.5	NS
Albumin (g/dL)	3.6±0.5	4.0±0.6	0.005
Platelet ($\times 10^3/\text{mm}^3$)	120±81	162±70	0.014
Child-Pugh classification			
NC/A/B/C, n (%)	2/14/1/0 (11.8/82.3/ 5.9/0)	463/299/76/24 (53.7/34.7/ 8.8/2.8)	NS
Virological data			
HBeAg, positive (%)	10 (58.8)	686 (79.6)	0.061*
HBV DNA (pg/mL)	176.7± 315.8	1320.1± 2,460.0	0.056
Follow-up period (years)	2.6±1.3	2.9±1.6	NS

AST, aspartate aminotransferase; ALT, alanine aminotransferase; NC, non-cirrhosis; HBe Ag, Hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NS, statistically non-significant ($p > 0.05$).

Values: mean±standard deviation.

*Statistical analysis: Student t-test or chi-square test.

1997 served as a control group since lamivudine was unavailable for the treatment of active hepatitis. Besides, six factors (gender, age, the platelet count, the alcohol history, serum albumin and ascites) were selected for conducting an adequate control study. Furthermore, the age variable was divided into three groups since age was known to be an independent risk factor for the development of HCC.¹⁸ The platelet count was also categorized into three groups since it is closely related to liver fibrosis.¹⁹ Although alcohol consumption over 80 g/day was recognized as having association with the development of HCC, we accepted 20 g/day as a cut-off for the

Table 6. Comparison of Background Factors between Patients Who Developed Hepatocellular Carcinoma and Those Who did not in the Lamivudine-Untreated Group

	Patients with HCC (n=157)	Patients without HCC (n=1,475)	P- values
Clinical data			
Age (years)	48.0±10.4	37.1±13.3	<0.001
Gender (M/F)	124/33 (79.0/21.0)	1043/432 (70.7/29.3)	0.032*
Family history, yes (%)	56 (35.7)	647 (43.9)	NS
Alcohol (≥20 g/day), n (%)	62 (39.5)	382 (25.9)	0.001*
Alcohol consumption (g/day)	41±59	24±49	<0.001
Interferon history, yes (%)	11 (7.0)	97 (6.6)	NS
Ascites, yes (%)	23 (14.6)	138 (9.4)	0.047*
Laboratory data			
AST (IU/L)	81±95	89±133	NS
ALT (IU/L)	81±137	108±175	0.070
Total bilirubin (mg/dL)	1.3±0.9	1.1±0.9	NS
Albumin (g/dL)	3.8±0.6	4.1±0.6	NS
Platelet (×10 ³ /mm ³)	134±71	188±85	<0.001
Child-Pugh classification			
NC/A/B/C, n (%)	56/67/ 30/4 (35.7/42.7/ 19.1/2.5)	995/279/ 156/45 (67.4/18.9/ 10.6/3.1)	0.005
Virological data			
HBeAg, positive (%)	64 (40.8)	705 (47.8)	NS
HBV DNA (pg/mL)	400.1± 1,140.9	640.1± 3,715.5	NS
Follow-up period (years)	6.0±4.4	5.3±4.7	NS

AST, aspartate aminotransferase; ALT, alanine aminotransferase; NC, non-cirrhosis; HBe Ag, Hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NS, statistically non-significant ($p > 0.05$).

Values: mean±standard deviation.

*Statistical analysis: Student t-test or chi-square test.

controlled study. This prevented patients who drank alcohol under 80 g/day alcohol from being misclassified as patients with negative alcohol history. As described in Tables 4 and 5, the patients who developed HCC drank larger amount of alcohol even though it was below 80 g/day.

This retrospective, matched case-controlled study showed that lamivudine reduced the incidence of HCC in patients with chronic hepatitis B (0.61 vs 2.16%/patients/year, respectively, $p=0.0117$). Liaw et al²⁰ reported that lamivudine decreased the progression of this disease in

patients with chronic hepatitis B and advanced liver disease, and it prevented complications such as hepatocellular carcinoma. However, the study population was rather small in order to evaluate the preventive effect of lamivudine on HCC significant statistical power. There were 5 patients who developed HCC during the first year of the study. If those 5 patients were to be excluded, the preventive effect of lamivudine on HCC became obscure as the p value was 0.052. (Piao et al²¹ reported that lamivudine did not accelerate HCC recurrence in the patients who developed HCC.)

The previously reported articles also showed controversial results on the preventive effect of lamivudine against HCC. Matsumoto et al²² in a multicenter retrospective study of 2,795 patients reported that lamivudine reduced the incidence of HCC in patients suffering from chronic hepatitis B. The present study in concordance with Matsumoto's results showed that lamivudine may prevent HCC in patients suffering from chronic hepatitis B. However, our results showed a slight difference from Matsumoto's results, which seemed to be caused by the characteristics of each study's patient group. The rate of HCC in the lamivudine group was 0.4% patients/year in Matsumoto's study, and it was 0.61% patients/year in ours. Although the baseline clinical characteristics of Matsumoto's patient group were similar to ours, there were more patients with a history of interferon therapy in Matsumoto's group than in our group (34.2% and 10.9%, respectively).

For the case-controlled study (Table 3), the levels of AST, ALT and HBV DNA in a lamivudine group were higher than those in the control group, and there were more HBe antigen positive patients in a lamivudine group than that in the control group. Since lamivudine has been used in general practice under the Korean National Health Insurance system, this is inevitable. The result seemed to be acceptable, despite of this difference. The incidence of HCC in the lamivudine group was lower than that in the control group even though hepatitis in the lamivudine group seemed to be active.

Although the mechanisms by which lamivudine prevents HCC in patients suffering from chronic hepatitis B are unclear, persistent viral suppression and decreased necroinflammation of the hepatocytes seem to be the main causes. Even though it has been reported that the transcription and expression of the X gene, which is related to HCC, was inhibited by lamivudine, definite relationship is still unclear.²³

The major drawback of lamivudine is the high rate of emergence of viral resistance. This was observed in

15-20% of patients after 1 year and it surmounted to 70% after 5 years of continued treatment.²⁴ As stated above, this study has a limitation as we didn't consider the viral resistance into account. After viral breakthrough occurred, we switched into or added adefovir dipivoxil. Since persistent viral suppression and decreased necroinflammation of hepatocytes seem to be the main mechanisms for preventing HCC, the effect of lamivudine on preventing HCC is thought to be limited to the period of viral suppression and the suppressed necroinflammation of hepatocytes. Therefore, the preventative effect on HCC does not seem to be a unique action of lamivudine, and other antiviral agents such as adefovir dipivoxil, entecavir and telbivudine are thought to have the equivalent effect, although further studies are needed pertaining this.

Several studies about interferon's preventive effect on HCC have been reported.^{25,26} Of these reports, only one randomized case-control study revealed that interferon had the preventive effect on HCC, but that study had the limitation due to a small study population.²⁵ Another study showed that the patients with a response to interferon displayed a preventive effect on HCC, but that study had the limitation of being an uncontrolled study.²⁶ Meta-analysis has shown that interferon has no or minimal preventive effect on HCC, but the responders do show a favorable effect.⁹

In conclusion, this retrospective, matched case-controlled study indicated that lamivudine might reduce the incidence of HCC in patients suffering from chronic hepatitis B. Further studies are needed to clarify the limitations of this study.

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