Antiviral efficacy of lamivudine versus entecavir in patients with hepatitis B virus-related advanced hepatocellular carcinoma

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ABSTRACT

Antiviral efficacy of lamivudine *versus* entecavir in patients with hepatitis B virus-related advanced hepatocellular carcinoma

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Background/Aims: Little information is available about the antiviral efficacy of lamivudine (LAM) and entecavir (ETV) in patients with hepatitis B virus (HBV)-related advanced hepatocellular carcinoma (HCC). Thus, we compared the antiviral efficacy of LAM and ETV in these patients.

Methods: The medical records of 134 antiviral therapy–naïve patients with HBV-related advanced HCC [modified Union for International Cancer Control (UICC) Tumor, Nodes, and Metastases (TNM) stages III–IV] treated between January 2005 and December 2009 were reviewed. After HCC diagnosis, 87 (64.9%) and 47 (35.1%) patients received LAM and ETV, respectively.

Results: The mean age of patients (115 men, 19 women) was 53 years.

Sixty-five (48.5%) and 69 (51.5%) patients had TNM stages III and IV HCC, respectively. Treatment outcomes during follow-up, including virologic, biochemical, and serologic responses and appearance of antiviral resistance, were similar in the LAM and ETV groups (all $p > 0.05$). Multivariate analysis identified Child–Pugh class, alpha-fetoprotein, and TNM stage as independent predictors of overall survival (all $p < 0.05$). Antiviral agent type (LAM *vs*. ETV) did not influence overall survival (median 9.6 months in LAM *vs*. 13.6 months in ETV group; $p = 0.493$). HCC treatment was not interrupted due to HBV flare up in any patient.

Conclusions: The antiviral efficacy of LAM and ETV was similar and the type of antiviral agent did not influence overall survival in patients with HBV-related advanced HCC. Thus, LAM, which is less expensive than ETV in Korea, might be sufficient to control HBV in these patients.

Key words : efficacy, entecavir, hepatitis B virus, hepatocellular carcinoma, lamivudine

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I. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and is characterized by low survival and a poor prognosis[1]. HCC is commonly detected at an advanced stage, and only 10–30% of HCC cases are eligible for curative surgical resection at the time of tumor diagnosis[2]. Although diverse therapeutic approaches, such as transarterial chemoembolization (TACE)[3], hepatic artery infusion chemotherapy[4,5], concurrent chemoradiation therapy[6], and sorafenib[7,8] have been attempted in advanced HCC patients, overall response rates have been unsatisfactory and the median survival time is less than 1 year from the time of initial diagnosis[6,9].

In particular, 70–80% of HCC patients in Asia have hepatitis B virus (HBV) infection, and a large number of patients with HCC are simultaneously diagnosed with HBV infection[10]. Previous studies have demonstrated that prolonged HBV suppression using antiviral therapy in patients with HBV-related HCC is equally important as treating the tumor[11], because the

maintenance of underlying liver function can assist in deciding HCC treatment strategies and improve overall survival[12].

Over the past two decades, antiviral therapy for patients with chronic hepatitis B (CHB) has improved with the use of nucleot(s)ide analogues (NUC) such as lamivudine (LAM) and entecavir (ETV); in Korea, these are usually selected as the first NUC. LAM was the first oral antiviral agent for HBV infection approved by the U.S. in 1995. This is the (–) enantiomer of 2-3 dideoxy-3-thiacytidine. Incorporation of the active triphosphate (3TC-TP) into growing DNA chains results in premature chain termination thereby inhibiting HBV DNA synthesis[17]. ETV, a deoxyguanine nucleoside analogue, is a selective inhibitor of the replication of HBV. *In vitro* studies showed that entecavir is more potent than lamivudine and adefovir, and is effective against lamivudine-resistant[17]. Although LAM is effective, well tolerated, and inexpensive, the emergence of LAM-resistant HBV mutants has been a major limitation of prolonged therapy[13]. Thus, LAM is not currently recommended as a first-line antiviral agent in most guidelines[14]. In contrast, although ETV is more expensive than LAM, current guidelines for antiviral therapy suggest that ETV should be considered as a first-line therapy for CHB because of its excellent efficacy in suppressing HBV DNA and its low resistance rate[15,16]. However, if antiviral therapy is started after the diagnosis of advanced HCC, the question remains whether LAM is inferior to ETV as a first-line antiviral therapy, because there is little chance of the development of LAM resistance

due to the short survival time of patients with advanced HCC. Thus, we compared the efficacy of LAM and ETV in antiviral therapy–naïve patients with HBV-related advanced HCC to demonstrate the potential of LAM as a first-line antiviral therapy.

II. MATERIALS AND METHODS

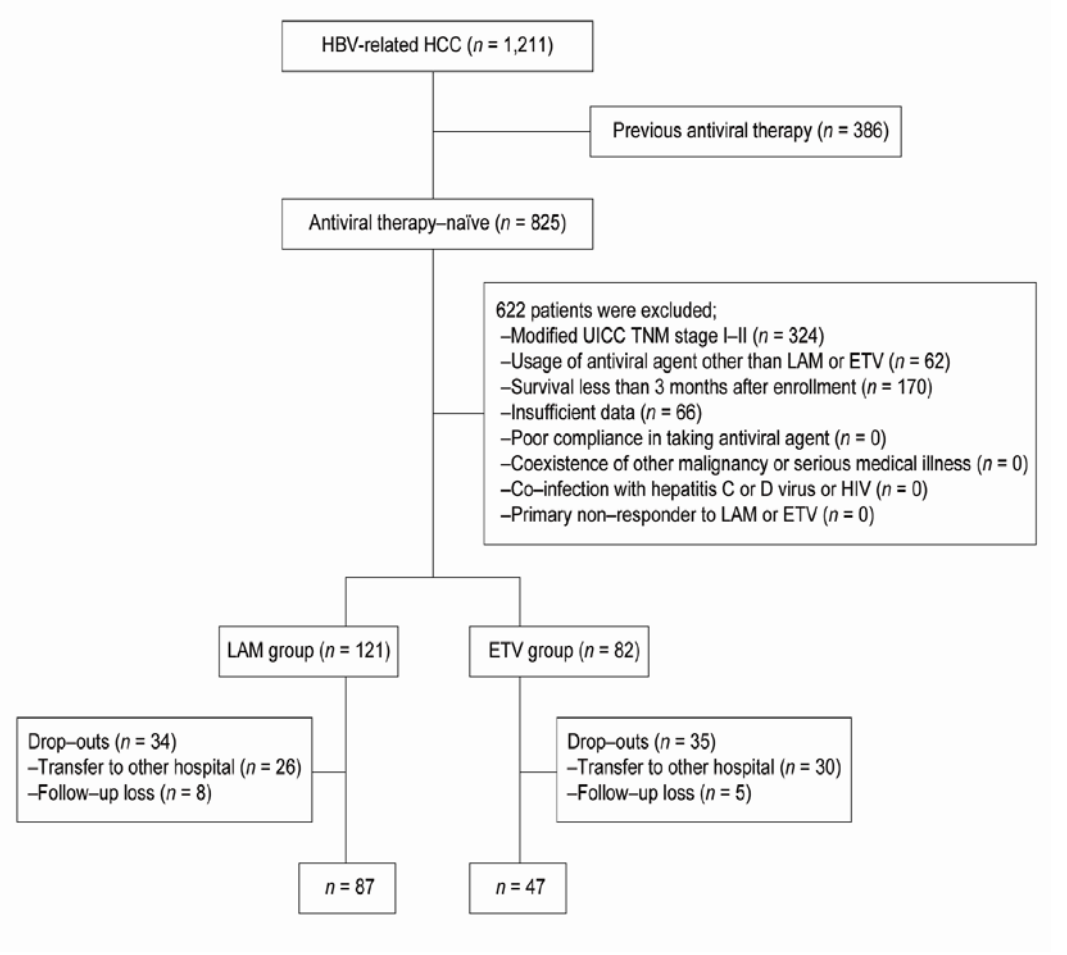
1. Patients

Between January 2005 and December 2009, a total of 825 antiviral therapy–naïve patients with HBV-related HCC visited the liver unit of Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. This study was conducted retrospectively by reviewing medical records. Our study protocol was consistent with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the independent institutional review board of our institute.

The exclusion criteria were: 1) previous antiviral therapy for CHB (interferon or NUC), 2) modified Union for International Cancer Control (UICC) Tumor, Nodes, and Metastases (TNM) stages I–II, 3) usage of antiviral agent other than LAM or ETV, 4) survival time of less than 3 months after enrollment, 5) insufficient data, 6) poor compliance with the antiviral drug regime, 7) coexistence of other malignancies or serious medical illness, 8) co-infection with hepatitis C or D virus or HIV, 9) primary non-responder to LAM or ETV, or 10) transfer to other hospital or loss of follow-up. A total of 134 patients were

included in the study sample (Figure 1).

Figure 1. Flow diagram of study population selection.



Abbreviations

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; UICC, Union for International Cancer Control; TNM, Tumor–Node–Metastasis; LAM, lamivudine; ETV, entecavir; HIV, human immunodeficiency virus.

2. Study design and definitions

The primary endpoint was comparison of the antiviral efficacy of LAM and ETV in antiviral therapy–naïve patients with HBV-related advanced HCC. To compare the efficacy of antiviral treatment, hepatitis B e-antigen (HBeAg), antibody to HBeAg (anti-HBe), HBV DNA, and alanine aminotransferase (ALT) levels were assessed at baseline and at months 3, 6, and 12. Biochemical data including ALT, aspartate aminotransferase (AST), total bilirubin, albumin, prothrombin time, and platelet count were collected at baseline.

The indication for antiviral treatment was based on the guidelines of the American Association for the Study of Liver Disease[17]. We defined evidence of liver cirrhosis as: 1) histologic confirmation by liver biopsy; 2) overt clinical manifestations of decompensation (Child–Pugh classes B and C); 3) current or past history of cirrhosis-related complications (e.g., ascites, variceal bleeding, or hepatic encephalopathy); and 4) platelet count <100,000/mm^3 with ultrasonographic findings suggestive of cirrhosis, including blunted or nodular liver edge accompanied by splenomegaly (>12 cm)[18].

During antiviral therapy, virologic response (VR) was defined as an HBV DNA level undetectable by quantitative polymerase chain reaction (PCR) assay (<12 IU/mL)[17]. Virologic breakthrough (VB) was defined as a confirmed increase in HBV DNA level of more than 1 $\log_{10}$ IU/mL compared with the nadir (lowest value) HBV DNA level on therapy[17]. Biochemical response (BR) was defined as a reduction in serum ALT level to within the normal range; a

threshold of 40 IU/L was used as the upper limit of normal (ULN)[17]. Biochemical breakthrough (BB) was defined as an increase in ALT above ULN after achieving normalization during continued treatment. HBeAg seroconversion was defined as the loss of HBeAg with the development of anti-HBe[17]. Genotypic resistance (GR) was defined as appearance of an HBV genome mutation that conferred resistance to antiviral agents[17]. A primary non-responder to LAM and ETV was defined as a <2 $\log_{10}$ IU/mL reduction of HBV DNA concentration over 6 months[17].

3. Diagnosis of HCC and staging system

The diagnosis of HCC was based on pathologic confirmation or typical appearance of HCC on either two dynamic imaging examinations (computed tomography and magnetic resonance imaging) or one dynamic technique with elevated serum alpha-fetoprotein (AFP; >400 ng/mL)[19]. HCC was staged using the TNM system, which was based on the 4th Japanese edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer[20].

4. Laboratory assays

HBV DNA levels were measured by quantitative PCR assay (Amplicor HBV Monitor Test; Roche Diagnostics, Basel, Switzerland; detection limit, ~12 IU/mL). Biochemical data including ALT, AST, total bilirubin, albumin, prothrombin time, and platelet count were measured using a sequential multiple

auto-analyzer (Hitachi Ltd., Tokyo, Japan). Serologic markers, including HBsAg, HBeAg, and anti-HBe, were determined using enzyme-linked immunoassays (Dade Behring, Marburg, Germany). For genotypic analysis, HBV DNA was extracted from serum samples using a commercial kit (Qiagen, Valencia, CA, USA) and analyzed by restriction fragment mass polymorphism[21,22].

5. Statistical analysis

Data are expressed as mean ± standard deviation or median (range). Serum HBV DNA concentrations were expressed on a logarithmic scale. Student's *t*-test for continuous variables and a chi-square test (or Fisher's exact test) for categorical variables were used to compare LAM and ETV groups. Overall survival rates were calculated by the Kaplan–Meier method and differences between groups were compared by the log-rank test. All two-sided *p* values were considered significant if less than 0.05. Data analyses were performed using SAS software (ver. 9.1.3; SAS Institute Inc., Cary, NC, USA).

III. RESULTS

1. Baseline characteristics

A total of 134 antiviral therapy–naïve patients with HBV-related advanced HCC were selected. After the diagnosis of HCC, 87 (64.9%) received LAM

(LAM group) and 47 (35.1%) received ETV (ETV group). The baseline characteristics of the LAM and ETV groups are shown in Table 1. The mean age of the patients (115 men and 19 women) was 53 years. Mean HBV DNA and ALT levels were 6.30 ± 1.50 $\log_{10}$ IU/mL and 61.5 ± 40.5 IU/L, respectively. HBeAg was positive in 82 (62.7%) patients and most (n = 98, 73.1%) had Child–Pugh class A liver function, whereas the other 36 (26.9%) patients had Child–Pugh class B liver function. Sixty-five (48.5%) and 69 (51.5%) patients had TNM stages III and IV HCC, respectively. Demographic and laboratory characteristics were similar between the LAM and ETV groups (all $p > 0.05$). In addition, tumor stage and treatment modalities of HCC did not differ significantly between the two groups (all $p < 0.05$) (5, 6). In the LAM group, 60, 42, and 25 patients were alive at months 3, 6, and 12, respectively; in the ETV group, 39, 26, and 17 patients were alive at months 3, 6, and 12, respectively. The median follow-up duration was 9.8 (range, 7.5–12.1) months.

Table 1. Baseline characteristics of the study population (*n*=134).

	Total (*n*=134)	LAM group (*n*=87, 64.9%)	ETV group (*n*=47, 35.1%)	*p* value
Age, years	53 ± 14	53 ± 15	53 ± 11	0.922
Male	115 (85.8)	78 (89.7)	37 (78.7)	0.118
Liver cirrhosis	96 (71.6)	59 (67.8)	37 (78.7)	0.229
Previous history of decompensation	7 (5.2)	4 (4.6)	3 (6.4)	0.107
Child-Pugh class, A/ B	98 (73.1)/ 36 (26.9)	63 (72.4)/ 24 (27.6)	35 (74.5)/ 12 (25.5)	0.841
Biochemical variables				
Alanine aminotransferase, IU/L	61.5 ± 40.5	70.6 ± 47.0	82.8 ± 40.0	0.980
Albumin, g/dL	3.80 ± 0.70	3.74 ± 0.70	3.79 ± 0.80	0.410
Total bilirubin, mg/dL	0.90 ± 0.60	0.90 ± 0.60	0.80 ± 0.60	0.073
Prothrombin time, INR	1.08 ± 0.12	1.10 ± 0.11	1.06 ± 0.20	0.679
Platelet count, 10^3/μL	147.00 ± 100.75	159.00 ± 110.00	136.00 ± 76.00	0.311
HBV DNA, $\log_{10}$ IU/mL	6.30 ± 1.50	6.42 ± 1.42	6.24 ± 1.52	0.208
HBeAg positivity	82 (62.7)	59 (67.8)	25 (53.2)	0.134
Alpha fetoprotein, ng/mL	369.94 (1.93–99336.54)	470.53 (2.09–99336.54)	226.74 (1.93 –83000.00)	0.698*
Tumor stages				
TNM stage, III/ IV	65 (48.5)/ 69 (51.5)	39 (44.9)/ 48 (55.1)	26 (55.3)/ 21 (44.7)	0.507
Treatment modality				0.868
TACE	46 (34.4)	28 (32.2)	18 (38.3)	
HAIC	41 (30.6)	29 (33.3)	12 (25.5)	
CCRT	37 (27.6)	23 (26.4)	14 (29.8)	
Systemic chemotherapy	9 (6.7)	6 (6.9)	3 (6.4)	
Best supportive care	1 (0.7)	1 (1.2)	0	

Variables are expressed as mean ± SD, median (range)*, or *n* (%).

LAM, lamivudine; ETV, entecavir; INR, international normalized ratio; HBeAg, hepatitis B e antigen; TNM, Tumor-Node-Metastasis; TACE, trans-arterial chemoembolization; HAIC, hepatic arterial infusional chemotherapy; CCRT, concurrent chemoradiation therapy.

2. Comparison of antiviral responses between lamivudine and entecavir

Outcomes of LAM and ETV therapy are presented in Table 2. During follow-up, HBV DNA was persistently reduced in both the LAM and ETV groups until 12 months after antiviral agent use. Although baseline HBV DNA levels were similar in the LAM and ETV groups, this level was significantly lower 12 months after antiviral therapy in the ETV group (p = 0.008). Furthermore, the ETV group showed a significantly greater reduction in HBV DNA level from baseline to 3 and 12 months in comparison with the LAM group (p = 0.003 and p = 0.028, respectively). Although VR was higher in the ETV group, this difference was not statistically significant at 3, 6, or 12 months (all $p > 0.05$). BR was calculated only for patients with baseline ALT levels $\geq 2 \times$ ULN [23 (26.4%) in the LAM group and 10 (21.3%) in the ETV group] and HBeAg seroconversion was counted only for HBeAg-positive patients [59 (67.8%) in the LAM group and 25 (53.2%) in the ETV group]. BR and HBeAg seroconversion did not differ significantly between the two groups at 3, 6, or 12 months (all $p > 0.05$).

Genotypic analysis was performed for patients who experienced VB, and GR was identified only in the LAM group (n = 3, 3.4%). Among these three patients, two had rtM204I/V and rtL180M, and one had only rtM204I. BB was found in the one patient with rtM204I (Table 2). All patients who had LAM–resistance mutations received rescue therapy with adefovir.

Table 2. Comparison of antiviral responses between lamivudine and entecavir.

Variables	LAM group (*n*=87, 64.9%)	ETV group (*n*=47, 35.1%)	*p* value
HBV DNA, $\log_{10}$ IU/mL			
Baseline	6.42 ± 0.86	6.24 ± 1.07	0.271
Month 3	4.99 ± 1.45	4.07 ± 1.25	0.001
Month 6	3.65 ± 1.70	3.09 ± 1.63	0.112
Month 12	2.97 ± 2.22	1.72 ± 1.09	0.008
Reduction of HBV DNA, $\log_{10}$ IU/mL			
Month 3	1.44 ± 1.38	2.17 ± 1.23	0.003
Month 6	2.69 ± 1.83	3.18 ± 1.78	0.220
Month 12	3.29 ± 2.42	4.62 ± 1.50	0.028
Virologic response			
Month 3	6 (6.9)	5 (10.6)	0.516
Month 6	17 (26.2)	12 (34.3)	0.489
Month 12	16 (48.5)	12 (57.1)	0.586
Biochemical response			
Month 3	19 (82.6)	5 (55.6)	0.176
Month 6	9 (90.0)	6 (100.0)	0.999
Month 12	4 (80.0)	5 (100.0)	0.999
HBeAg seroconversion			
Month 3	2 (3.1)	1 (4.2)	0.803
Month 6	4 (8.5)	2 (11.8)	0.699
Month 12	4 (17.4)	2 (18.2)	0.957
Antiviral resistance			
GR + VB	3 (3.4)	0 (0)	0.552
GR + VB + BB	1 (1.5)	0 (0)	0.999
Hepatitis flare[a]	0 (0)	0 (0)	0.999

Variables are expressed as mean ± SD or n (%).

LAM, lamivudine; ETV, entecavir; HBeAg, hepatitis B e antigen; GR, genotypic resistance; VB, virologic breakthrough; BR, biochemical breakthrough.

Hepatitis flarea was defined as the elevation of alanine aminotransferase (ALT) level to more than 10 times the upper normal limit.

3. Causes of death during study period

Seventy-six patients in the LAM group and 33 in the ETV group died during the study period (Table 3). Fifty (65.8%) patients in the LAM group and 22 (66.7%) in the ETV group died of HCC progression. One patient died of liver failure after TACE for recurrent HCC in the LAM group. However, no patient in either group died of liver failure due to hepatitis B flare up. The causes of death did not differ between the LAM and ETV groups ($p = 0.628$).

Table 3. Causes of death during study period.

Variables	LAM group (*n*=76)	ETV group (*n*=33)	*p* value
Disease progression	50 (65.8)	22 (66.7)	0.628
Infection (septic shock)	5 (6.5)	5 (15.0)	
Bleeding (hypovolemic shock)	10 (13.2)	2 (6.1)	
Treatment-related	1 (1.3)	0 (0)	
Hepatitis flare up	0 (0)	0 (0)	
Unidentified	10 (13.2)	4 (12.2)	

Variables are expressed as *n* (%).

4. Multivariate Cox regression analysis of covariates predicting overall survival

Univariate analysis identified Child–Pugh class (p = 0.002), initial AFP level (p = 0.001), and TNM stage (p = 0.001) as significant variables, as did a subsequent multivariate analysis to identify independent predictors of overall survival: Child–Pugh class [hazard ratio (HR), 1.518; 95% confidence interval (CI), 1.001–2.301; p = 0.049), initial AFP level (HR, 1.000; 95% CI, 1.000–1.000; p = 0.008), TNM stage (HR, 1.924; 95% CI, 1.435–2.579; p = 0.001; Table 4). However, the type of antiviral agent did not influence overall survival (median 9.6 months in the LAM group *vs*. 13.6 months in the ETV group; log-rank test, p = 0.495).

Table 4. Multivariate Cox regression analysis of covariates predicting overall survival.

	Univariate	Multivariate		
	p value	Hazard ratio	95% confidence interval	*p* value
Age, years	0.092			
Male	0.817			
Liver cirrhosis	0.343			
Child-Pugh class, B *vs.* A	0.002	1.518	1.001 - 2.301	0.049
Alanine aminotransferase, IU/L	0.264			
HBV DNA, $\log_{10}$ IU/mL	0.101			
HBeAg positivity	0.467			
Alpha fetoprotein, ng/mL	0.001	1	1.000 - 1.000	0.008
Antiviral treatment, LAM *vs.* ETV	0.495			
TNM stage, IV *vs.* III	0.001	1.924	1.435 - 2.579	0.001

HBeAg, hepatitis B e antigen; LAM, lamivudine; ETV, entecavir; TNM, Tumor-Node-Metastasis.

Reference values: Child-Pugh class A and TNM stage III.

IV. DISCUSSION

Current treatment of CHB with NUCs rarely eradicates HBV[21], necessitating long-term therapy to avoid viral reactivation and liver disease progression[23-25]. However, long-term antiviral therapy increases the chance of genotypic resistance, which is generally associated with a poorer clinical outcome[26]. Among NUCs, resistance to LAM occurs most frequently and is observed in up to 80% of patients treated for 5 years[27,28]. In contrast, long-term studies of ETV in NUC-naïve patients demonstrated that resistance remained low (1.2%) after 6 years of therapy[29]. Furthermore, no tenofovir resistance occurred after 4 years of NUC treatment[30]. Thus, ETV and tenofovir, with high genetic barriers to the development of resistance, are preferred for first-line antiviral therapy in patients with CHB.

Generally, antiviral therapy in patients with HBV-related HCC has been regarded as being equally important as the treatment of HCC[11], because antiviral therapy can improve overall survival by maintaining adequate residual liver function[12] and can affect the selection of an optimal HCC treatment modality. Furthermore, during cytotoxic chemotherapy or locoregional therapy for HCC[31-35], antiviral therapy is required in patients with HBV-related HCC to reduce the incidence and severity of potentially life-threatening HBV reactivation[35], thereby preventing the delay or premature discontinuation of anti-cancer therapy. In this regard, Jang *et al.*[31] proposed that a baseline HBV DNA level $>10^4$ copies/mL and the treatment chosen were independent

predictors of HBV reactivation during HCC therapy, and found a significant dose-risk relationship between the degree of treatment intensity and HBV reactivation. Thus, antiviral therapy may render patients with HBV-related HCC more tolerant to cytotoxic HCC treatments and may lead to a better prognosis.

Several studies have investigated the efficacy of antiviral therapy in patients with HCC[12,36]. Jin *et al*.[37] reported that the efficacy of ETV therapy with respect to virologic, serologic, and biochemical responses was similar in CHB patients with and without HCC. Kim *et al*.[11] reported similar viral and biochemical effects of LAM in CHB patients with and without HCC. Woo *et al*.[38] reported that clevudine had comparable antiviral and biochemical effects in CHB patients with and without HCC. If HCC is diagnosed in patients with CHB who are receiving ongoing antiviral therapy using NUC, the same drug can be used continuously. Likewise, if newly diagnosed HCC is at an early stage with expected long-term survival and is eligible for curative treatment, the choice of antiviral agent would be the same as in CHB cases. However, the optimal antiviral agent to use as the first-line regimen in antiviral therapy–naïve patients with newly-diagnosed HBV-related advanced HCC who are not eligible for curative treatment remains to be determined. We thus aimed to compare the efficacy of LAM and ETV, which are widely used in South Korea, in patients with HBV-related advanced HCC.

The antiviral efficacy and development of antiviral resistance during HCC treatment did not differ significantly in the LAM and ETV groups. In our study,

no HBV flare up or interruption of HCC treatment due to hepatic dysfunction occurred in either group. Furthermore, overall survival in the LAM and ETV groups was similar (median 9.6 *vs*. 13.6 months; log-rank test, $p = 0.493$). These results indicate that the antiviral efficacy of LAM, which has a low genetic barrier to resistance and low cost, as the first-line agent was not inferior to that of ETV, which has a high genetic barrier to resistance and high cost, in controlling HBV in patients with HBV-related advanced HCC. Thus, our report may assist in choosing an antiviral agent for newly diagnosed HBV-related advanced HCC, especially in developing countries where cost is an issue.

In our study, GR with VB was identified in only three (3.4%) patients in the LAM group, which is significantly lower than found in CHB patients without HCC[17]. This difference can be explained in part by the exclusion of patients who died before experiencing GR. This result also supported the argument that the development of antiviral resistance is less important in patients with advanced HCC who have short survival times.

V. CONCLUSION

In conclusion, we demonstrated that LAM, which has a low genetic barrier to resistance and low cost, is sufficiently efficacious as the first-line antiviral agent in treating patients with HBV-related advanced HCC when compared with ETV, which has a high genetic barrier to resistance and high cost. A further large-scale prospective study is needed to determine the efficacy of LAM and

ETV in patients with HBV-related advanced HCC.

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ABSTRACT(IN KOREAN)

B형 간염으로 인한 진행성 간세포암에서 라미부딘과 엔테카비어의 항바이러스 효능 비교

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신 혜 선

연구배경 : B형 간염으로 인한 진행성 간세포암 환자에서 라미부딘과 엔테카비어의 항바이러스 효능에 대한 연구는 아직 미흡한 실정이다. 따라서 본 연구에서는 이러한 환자군에서 두 약제의 항바이러스 효능을 비교해 보고자 하였다.

방법 : 2005년 1월부터 2009년 12월 사이에 B형 간염으로 인한 진행성 간세포암 (TNM 병기 3-4기)을 진단받은, 항바이러스 치료를 받은 적 없는 134명의 환자를 대상으로 후향적 연구를 진행하였다. 대상 환자 중 87명 (64.9%)은 라미부딘을 처방 받았고, 47명 (35.1%)은 엔테카비어를 처방 받았다.

결과 : 대상 환자의 평균 연령은 53세였다. 65명 (48.5%)은 TNM 병기 3기였고, 69명 (51.5%)은 TNM 병기 4기였다. 대상 환자의 바이러스적, 생화학적, 혈청학적 반응과 항바이러스

치료에 대한 내성 발현율은 두 군 사이에 유의한 차이를 보이지 않았다. 다변량 분석을 하였을때 전체 생존율에 독립적으로 영향을 주는 요인은 Child-Pugh class, 알파 태아단백, TNM 병기로 나타났다. 라미부딘과 엔테카비어중 어떤 항바이러스제로 치료를 했는지는 전체 생존율에 영향을 주는 요인이 아니었다. (9.6 개월 *vs.* 13.6 개월, log-rank: $p = 0.493$). 두 군 모두에서 간세포암 치료를 받는 동안 B형 간염의 악화를 보인 환자는 없었다.

결론 : 진행성 간세포암 환자에서 라미부딘과 엔테카비어의 항바이러스 효과 및 B형 간염 악화 예방 효과는 차이가 없다.

핵심되는 말 : 항바이러스 효능, 엔테카비어, B형 간염 바이러스, 간세포암, 라미부딘