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Original Article

Lamivudine Treatment in Patients with HBV-related Hepatocellular Carcinoma-using an Untreated, Matched Control Cohort

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Lamivudine is widely used to treat patients with hepatitis B. However, the outcomes in patients with hepatocellular carcinoma (HCC) treated with lamivudine have not been established. This study was conducted to evaluate the outcomes of lamivudine treatment for patients with HCC using an untreated, matched control group. Thirty patients with controlled HCC orally received lamivudine. As controls, 40 patients with HCC who were not treated with lamivudine and matched for clinical features were selected. The lamivudine-treated and untreated groups were compared with respect to changes in liver function, HCC recurrence, survival, and cause of death. In the lamivudine-treated group, there was significant improvement in the Child-Pugh score at 24 months after starting treatment, while no improvement was observed in the untreated group. There was no significant difference in the cumulative incidence of HCC recurrence and survival between the groups. However, there was a significant difference in the cumulative incidence of death due to liver failure ($P = 0.043$). A significant improvement in liver function was achieved by lamivudine treatment, even in patients with HCC. These results suggest that lamivudine treatment for patients with HCC may prevent death due to liver failure. Further prospective randomized studies using a larger number of patients are required.

Key words: liver failure, Child-Pugh score, recurrence, survival, resistant mutant

Lamivudine inhibits DNA synthesis by terminating proviral DNA chain elongation through interference by the reverse transcriptase activity of hepatitis B virus (HBV) DNA polymerase. Lamivudine has been shown to be effective for patients with chronic hepatitis (CH) B in several randomized, controlled trials[1, 2]. These studies have shown lamivudine to be effective in suppressing HBV DNA replication. Since lamivudine is well-tolerated and has few adverse effects, it has been widely used to treat hepatitis B including cirrhosis. Even in patients with advanced, decompensated liver disease, the beneficial effects of lamivudine treatment have been reported in several studies [3-6]. These studies have shown the efficacy of lamivudine in improving liver func-

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tion through tests and the Child-Pugh (C-P) score [7]. However, the efficacy and outcome of lamivudine treatment in patients with HCC have not yet been established.

In the present study, we examined the outcome of lamivudine treatment for patients with HCC in terms of liver function based on the C-P score and survival by comparison with a matched lamivudine-untreated cohort.

Materials and Methods

Cases and controls. Between January 2001 and April 2004, 1813 patients with hepatitis B surface antigens (HBsAg) were diagnosed as having CH, liver cirrhosis (LC), or HCC in hospitals of the Okayama Hepatitis Research Group consisting of 18 institutes in Japan. Of the 1813 patients with HBsAg, 1288 patients were diagnosed as having CH, 376 patients, LC, and 149 patients, HCC. Of the 149 patients with HCC, 41 (28%) patients orally received 100 mg of lamivudine daily after HCC treatment, and 108 (72%) did not. All of the lamivudine-treated patients had tested positive for HBV DNA in serum and with fluctuated alanine aminotransferase (ALT) before starting lamivudine. HCC was controlled by local ablation, trans-arterial chemoembolization (TAE), and surgery. The state of uncontrolled HCC was defined as remnant viable HCC, main portal vein invasion, and distant metastasis. Of the 41 patients treated with lamivudine, 30 were controlled for HCC and enrolled as subjects and 11 were excluded because of uncontrolled HCC (Fig. 1). As controls, selected 40 patients, who were controlled for HCC over a similar period of admission, and matched for age, gender, baseline C-P score, HCC stage[8], and Cancer of the Liver Italian Program (CLIP) score [9]. These patients were selected from 73 patients who had completed HCC therapy but not been treated with lamivudine (Fig. 1). Thus, our study design used an untreated, matched control cohort. Patients with any other viral coinfection, including the human immunodeficiency virus, hepatitis D virus, and hepatitis C virus, were excluded. None of the patients received transjugular intrahepatic portosystemic shunt, surgical portosystemic shunt, or splenectomy.

The following clinical data were collected: age, sex, family history, alcohol abuse, ascites, and encephalopathy. Family history was defined as the existence of HBV-related liver disease in a blood relation and daily alcohol consumption greater than 50 g of ethanol. All patients enrolled in this clinical trial gave written informed consent. The study design was approved by local ethics committees.

Markers of hepatitis virus infection and liver function. Hepatitis B serologies, including HBsAg, Hepatitis B e antigen (HBeAg), and antibody to HBeAg (anti-HBe) were measured using commercially available enzyme-linked immunosorbent assay. The HBV DNA level was measured using transcription-mediated amplification assay (TMA, SRL, Tokyo, Japan) or PCR assay (Amplicor HBV Monitor assay, SRL) and expressed as log copies/ml. The sensitivity of the assay was approximately 500–5000 copies/ml. Serum alanine aminotransferase (ALT), albumin (Alb), total bilirubin (T. Bil), prothrombin time (PT), and platelet count (PLT) were measured using standard laboratory procedures.

Follow-up. We examined clinical features such as ascites and hepatic encephalopathy by physical findings, and laboratory examinations of ALT, PT, Alb, T.Bil, and PLT every 3 months after enrollment. The C-P score was calculated at baseline and every 3 months during follow-up. The stage of hepatic encephalopathy used in the C-P scoring system was based on Gitlin's

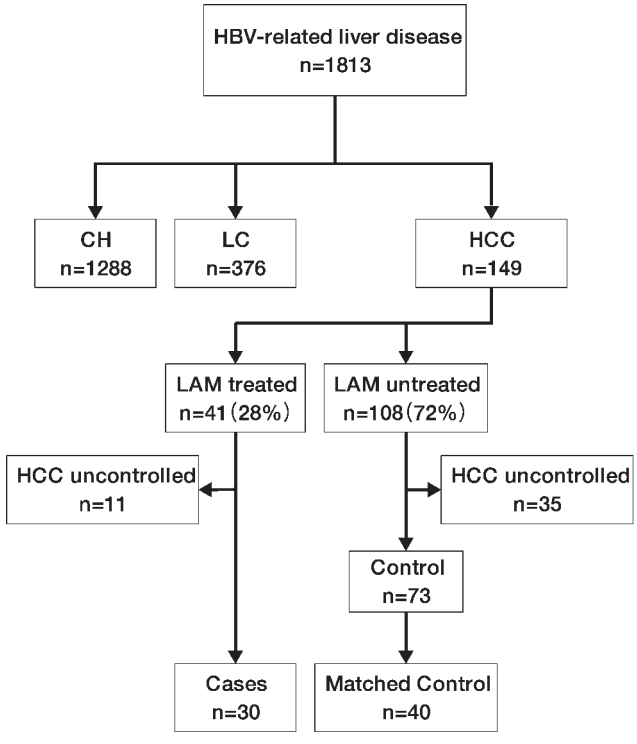


Fig. 1 Schematic flow chart of patient enrollment.

classification [10]. Virologic data including quantitative HBV DNA, HBeAg, and anti-HBe were also assessed every 3 months. Patients were monitored for the emergence of a lamivudine-resistant mutant based on serial HBV DNA and ALT levels. The patients were studied using real-time abdominal ultrasonography (US) or computed tomography (CT) every 3 or 6 months. HCC recurrence was diagnosed as tumor progression in different regions or in local regions. Recurrent HCC of fewer than 3 cm and less than 3 nodules were treated by local ablation, and if the recurrence showed more HCC lesions, treatment by TAE or trans-arterial chemo-infusion was added.

In the case of patient death, the cause of death was examined in detail. Death by liver failure was defined as controlled HCC and development of jaundice, ascites, and hepatic encephalopathy. On the other hand, death by HCC was defined as uncontrolled HCC with or without signs of liver failure.

Statistical analysis. Continuous variables are expressed as mean +/− SD or median and range. Fisher's exact test, the Student's *t*-test, and the Mann-Whitney U-test were performed as appropriate. All significance levels were determined using two-tailed tests. The lamivudine-treated and untreated groups were compared with respect to the laboratory data, the C-P score, virologic markers, and the emergence of a lamivudine-resistant mutant, HCC recurrence, treatment

Table 1 Baseline clinical and virologic characteristics of lamivudine-treated and untreated patients

	Lamivudine-treated Group	Untreated Group	*p*-values
Patients, n	30	40	
Clinical data			
Age (years) †	59 ± 12	58 ± 10	n.s.
Sex (M/F)	23/7	29/11	n.s.
Family history, n (%)	15 (50)	19 (48)	n.s.
Alcohol consumption, n (%)	7 (23)	18 (45)	0.061
Ascites, n (%)	4 (13)	9 (23)	n.s.
Encephalopathy, n (%)	0 (0)	0 (0)	n.s.
Laboratory data			
Total Bilirubin (mg/dl) †	1.6 ± 1.1	1.5 ± 1.9	n.s.
ALT (IU/L) †	88 ± 81	62 ± 53	0.11
Albumin (g/dl) †	3.3 ± 0.88	3.4 ± 0.49	n.s.
PT (%)†	71 ± 16	72 ± 22	n.s.
Platelet count ($\times 10^3/mm^3$) †	104 ± 71	120 ± 63	n.s.
ICG(R15) (%)	24 ± 14	26 ± 19	n.s.
Child classification (A/B/C)	18/11/1	22/17/1	n.s.
C-P score‡	6 (5–10)	6 (5–10)	n.s.
Virologic data			
HBeAg, positive (%)	9 (30)	16 (40)	n.s.
HBV DNA (log copies/ml) ‡	6.1 (3.7–8.4)	6.5 (3.7–7.5)	n.s.
HCC			
Size (mm) ‡	23 (10–40)	25 (10–127)	n.s.
Number‡	1 (1–3)	1 (1–3)	n.s.
HCC stage (1/2/3/4)	14/9/4/3	17/16/7/0	n.s.
CLIP score (0/1/2/3/4)	15/10/4/0/1	15/15/7/3/0	n.s.
CLIP score‡	1 (0–3)	0.5 (0–4)	n.s.
Initial treatment for HCC (Ablation/TAE/Operation)	4/14/12	12/18/10	n.s.

No statistically significant difference was found between the 2 groups.

ALT, alanine aminotransferase; CLIP score, cancer of the liver Italian program score; C-P score, Child-Pugh score; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; ICG (R15), indocyanine green retention rate at 15 min; PT, prothrombin time; TAE, transarterial chemo-embolization.

†The data are expressed as mean and standard deviation.

‡The data are expressed as medians and ranges in the parentheses.

for recurrence, survival, and cause of death. The Kaplan-Meier methods were used to calculate the cumulative incidence of HCC recurrence and death during follow-up. Comparison of the survival rates obtained was performed by a log-rank test. Statistical analysis was performed with JMP software 5.01J (SAS Institute Inc., Cary, NY, USA).

Results

Baseline characteristics. The baseline characteristics of the lamivudine-treated and untreated groups are summarized in Table 1. The 2 groups were matched by age, gender, C-P scores, stage of HCC, and CLIP score. There was no prominent difference in the baseline virologic and clinical characteristics between the groups. However, there was tendency to introduce lamivudine treatment in patients with ALT elevation and without alcohol consumption.

Virologic markers and development of lamivudine resistance. Patients were observed for an average follow-up period of 24 months after starting treatment with lamivudine, while in the untreated group, the average observation period was 31 months after complete HCC treatment. HBV DNA decreased and became undetectable by TMA or PCR assay in all treated patients within 6 months after the initiation of lamivudine (Fig. 2). Two of 9 (22%) treated patients who were initially HBeAg-positive lost HBeAg and sustained seroconversion from HBeAg to anti-HBe during the follow-up period. On the other hand, none of the patients showed HBV DNA in the tests or HBe seroconversion in the untreated group.

Among the 30 treated patients, 5 (17%) developed lamivudine resistance, and the cumulative incidence of the development of resistance at 12 and 24 months was 7.6% and 21%, respectively. Four of these 5 patients maintained stable liver function, and the additional administration of 10 mg per day of adefovir dipivoxil was required in 1 patient because of breakthrough hepatitis.

Changes in liver function and C-P score. In the 30 treated patients, each parameter of Alb, PT, T. Bil, ALT, and PLT improved after starting lamivudine treatment (Fig. 2), and there was a marked improvement in liver function after 24 months. Only 1 patient exhibited a deterioration in liver function after the development of lamivudine resistance; this patient was then treated with adefovir dipivoxil. In contrast, there

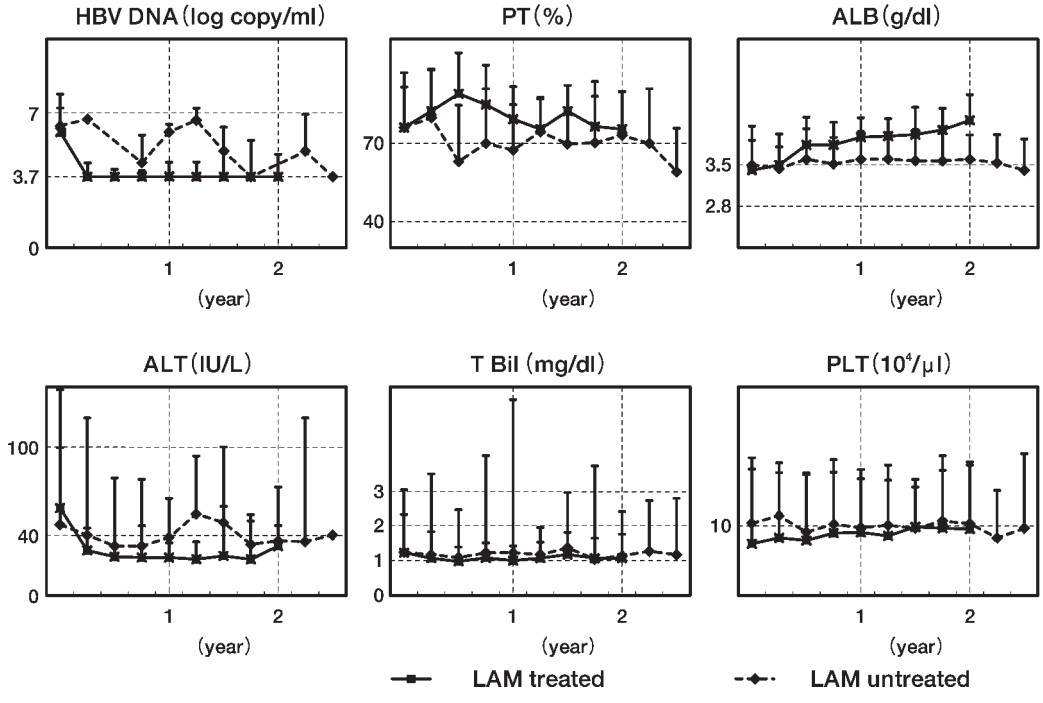


Fig. 2 Changes in laboratory data in the lamivudine-treated and untreated groups.

was no improvement in liver function in the controls (Fig. 2). Improvement in C-P score was also observed in all lamivudine-treated patients, while no improvement was observed in the controls. However, the full extent of the improvement took 6 months or longer in most patients after starting lamivudine treatment (Fig. 3). The median change in the Child-Pugh score was a -1.0 regression in the treated group versus a $+0.5$ aggravation in the control group ($P < 0.01$) after 24 months.

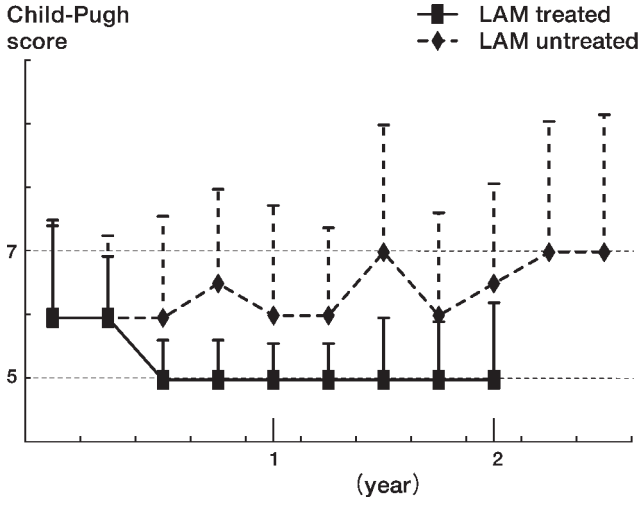


Fig. 3 Changes in the Child-Pugh score in the lamivudine-treated and untreated groups.

HCC recurrence, treatment for recurrence, survival, and cause of death. During the follow-up, the cumulative incidence of HCC recurrence was similar between the lamivudine-treated and untreated groups (Fig. 4). In the treated group, 14 patients experienced a recurrence of HCC. The incidence of HCC recurrence at 12 and 24 months after enrollment was 25 % and 54%, respectively. All of these patients then received local ablation and/or TAE. In contrast, 26 patients in the control group experienced HCC recurrence. The incidence of recurrence at 12, 24, and 36 months was 42%, 59%, and 78%, respectively. However, 6 (25%) of the 26 patients were unable to receive local treatment due to severe liver failure. Of these 6 patients, 4 (67%) died during follow-up, all due to HCC progression.

During the follow-up period, 2 patients (6.7%) died in the treated group, and the cumulative incidence of death at 12 and 24 months was 0% and 8.7%, respectively. On the other hand, 12 patients (30%) died in the untreated group, and the incidence of death at 12, 24, and 36 months was 7.6%, 13%, and 34%, respectively. The cumulative incidence of death was not significantly different between the groups, although there was a trend toward an improvement in survival rate in the treated group compared with the untreated group ($P = 0.12$) (Fig. 5).

Two patients died of HCC progression in the treated

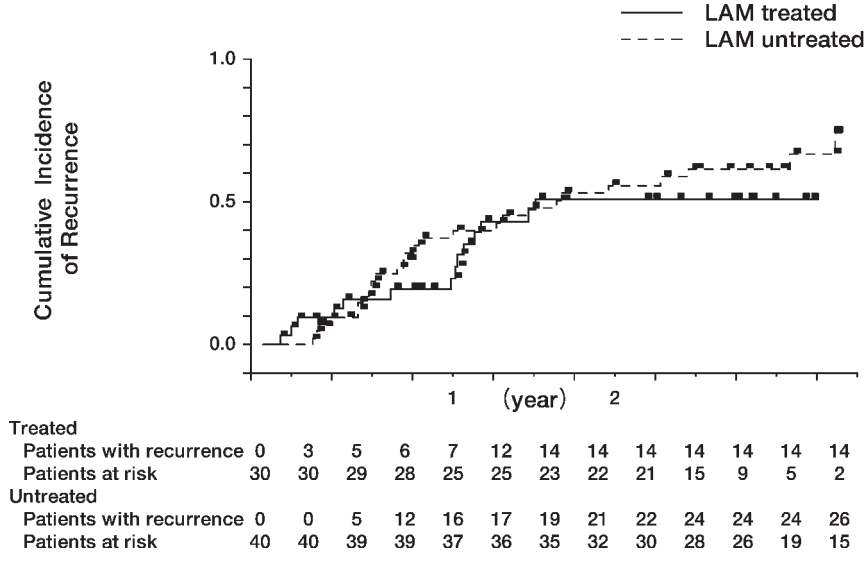
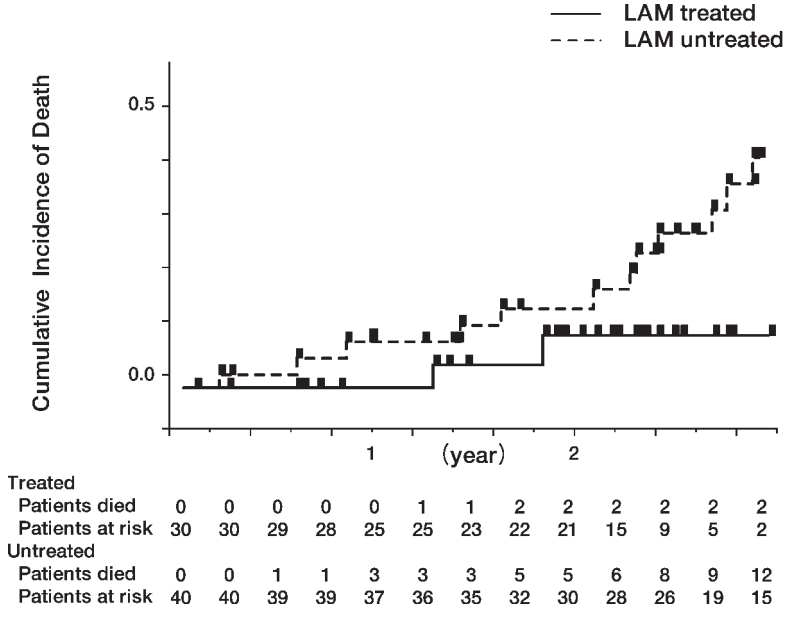


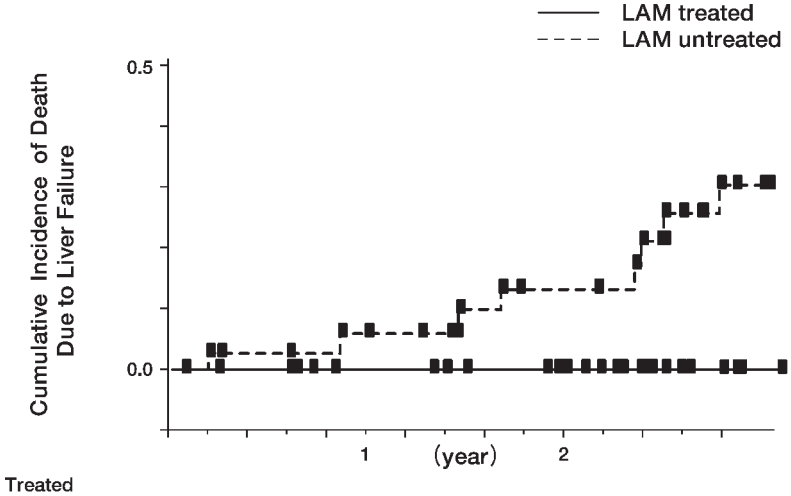
Fig. 4 Cumulative incidence of HCC recurrence in the lamivudine-treated and untreated groups.

groups, while 8 (67%) died of liver failure and 4 patients (33%) of HCC progression in the control group. Despite the additional treatment and control for HCC recurrence in the 8 patients who died of liver failure, 2 took a turn for the worse as a result of hemorrhagic shock caused by rupture of esophageal varices, and the other 6 progressed to decompensated liver cirrhosis. As such, none of the patients treated with lamivudine died of liver failure, and there was a significant difference in the cumulative incidence of death due to liver failure between the lamivudine-treated and untreated groups ($P = 0.043$) (Fig. 6).



Treated													
Patients died	0	0	0	0	0	1	1	2	2	2	2	2	2
Patients at risk	30	30	29	28	25	25	23	22	21	15	9	5	2
Untreated													
Patients died	0	0	1	1	3	3	3	5	5	6	8	9	12
Patients at risk	40	40	39	39	37	36	35	32	30	28	26	19	15

Fig. 5 Cumulative incidence of death in the lamivudine-treated and untreated groups.



Treated													
Patients died	0	0	0	0	0	0	0	0	0	0	0	0	0
Patients at risk	30	30	29	28	25	25	23	22	21	15	9	5	2
Untreated													
Patients died	0	0	1	1	2	2	3	4	4	4	6	7	8
Patients at risk	40	40	39	39	37	36	35	32	30	28	26	19	15

Fig. 6 Cumulative incidence of death due to liver failure in the lamivudine-treated and untreated groups.

Discussion

The reliable benefits of lamivudine treatment in patients with decompensated cirrhosis have been suggested by several uncontrolled [4, 5] and controlled studies [3]. This study includes an untreated, matched control cohort, demonstrating the potential benefit of lamivudine treatment for patients with HCC. The present data clearly show that lamivudine treatment results in suppressing viral replication and improving liver function and C-P score, even in patients with HCC.

In the lamivudine-treated group, death due to liver failure was not observed, and there was a significant difference in the incidence of death due to liver failure between the lamivudine-treated and untreated groups. Case reports of patients with HCC treated with lamivudine indicate that the patients were successfully treated by hepatic resection or intra-arterial chemotherapy, despite experiencing liver failure or advanced HCC before treatment with lamivudine [11, 12]. Although these were case reports, it is suggested that the administration of lamivudine reduces serum HBV DNA levels and improves liver function in patients with HCC. This study demonstrates, for the first time, based on a case-control study using a considerable number of patients, that lamivudine treatment may be useful in preventing death due to liver failure in patients with HCC. There are more patients with HCC who die of liver failure than those who die of HCC, as demonstrated in the present observation of the untreated cohort. As such, inhibition of death due to liver failure in patients with HCC is of clinical importance.

The relationship between the development of HCC and lamivudine treatment has yet to be clarified. The present data indicate that lamivudine treatment does not accelerate HCC recurrence. These data are consistent with previous findings demonstrating that lamivudine treatment is not associated with increased HCC development in patients with cirrhosis during a median follow-up of 18 months [13].

Inhibition of viral replication by lamivudine treatment results in histological improvement during long-term therapy [14]. The present data confirm the association between the suppression of viral replication and improvement in liver function, even in patients with HCC. In subjects presenting HCC recurrence, the remaining liver function is an important factor in selecting further treatment for HCC. Since several re-treatment options for HCC can be selected for lamivudine-treated patients, these options may contribute to the prevention of early cancer death, resulting in a possible improvement in survival.

Since liver transplantation from cadaveric donors for end-stage liver disease is rarely carried out in Japan due to the scarcity of cadaveric liver grafts, living-donor liver transplantation (LDLT) is the more frequently performed procedure, even in patients with HCC [15]. Furthermore, patients with HBV often have difficulty in receiving LDLT because of the high prevalence of HBV in relatives who are potential donors. Thus, lamivudine treatment would be useful for end-stage liver disease such as for patients with HCC for whom donor liver availability is limited.

One of the major problems during prolonged lamivudine treatment is the emergence of lamivudine-resistant mutant HBV [16–18]. During therapy, 15% of patients with chronic hepatitis develop the mutant each year [19], and the incidence of the mutant increases year after year [20]. The differences in the development of drug resistance between patients with and without cirrhosis are reportedly negligible [21]. The rate of mutant development in this study was very similar to that previously reported in patients with chronic hepatitis [20]. Only one patient required administration of adefovir dipivoxil [22, 23], but the others were able to control liver function without additional antiviral therapy. Thus, none of the patients who developed the lamivudine-resistant mutant died of liver failure.

This study was conducted in a small number of patients observed for a limited follow-up period. Thus, an additional prospective randomized controlled study using a larger number of patients is required to confirm the prevention of death due to liver failure by lamivudine treatment and to determine the influence of lamivudine treatment on HCC recurrence.

In conclusion, inhibiting viral replication by treatment with lamivudine results in a significant improvement in liver function, even in patients with HCC. Lamivudine treatment for patients with HCC may prevent death due to liver failure.

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General Hospital, Fukuyama National Hospital, Shigei Medical Research Institute, Takahashi Central Hospital, Nippon Kokan Fukuyama Hospital, Iwakuni National Hospital, Akaiwa City Ishikai Hospital, Mihara Red Cross Hospital, Mizushima Central Hospital, and Teraoka Memorial Hospital.

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