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Follow–up Study on Recurrence of Hepatocellular Carcinoma in Patients Administrated ACE Inhibitor

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Abstract：Background/Aims：Hepatocelluar carcinoma（HCC）has a higher rate of recurrence after treatment because of its multiple central growth and intrahepatic metastasis in comparison to other cancers. Recent studies have shown angiotensin converting enzyme（ACE）inhibitors to reduce the mortality rate of cancer through its inhibitory effect on neovascularization. We therefore examined effects of ACE inhibitors on the growth of HCC which accompanies profound neovascularization. The inhibition of the growth of cancer by ACE inhibitors is said to induce neovascularization. ACE inhibitors are therefore expected to be effective for the treatment of HCC with many newly formed blood vessels. Method：Of the 318 patients who were diagnosed with HCC and received medical treatment initially, 32 patients with a tumor diameter of less than 5 cm and hepatic reserve capacity classified as A or B according to the Child ś classification, who take only one kind of antihypertensive agent because of hypertension developing complication, were selected as the subjects. Ten of those patients were taking ACE inhibitors while and 22 patients were taking calcium antagonists. Results：Concerning the clinical features, significant differences were found in the diastolic pressure but not in the number of tumors and tumor diameter between the two groups. The 3–year recurrence rate was 67.5% in the ACE inhibitor group and 62.6% in the calcium antagonist group（p＝0.851）. Conclusion：According to the retrospective investigation, no significant difference in the 3–year recurrence rate was found between the group of ACE inhibitor and calcium antagonist.

Key words：Angiotensin converting enzyme（ACE）inhibitor, Hepatocelluar carcinoma（HCC）, Calcium antagonist, Recurrent rate of HCC

Introduction

A high percentage of hepatocellular carcinoma（HCC）patients exhibit viral hepatitis and liver cirrhosis; an average of approximately 20% of patients experience recurrent HCC lesions every year after treatment.[1)–4)] However, no drugs significantly inhibiting the recurrence are yet available.

In 1998 Lever *et al.* reported that long–term administration of ACE inhibitors resulted in a decrease in the mortality of cancer.[5)] In 2001, Yoshiji *et al.* examined the effects of ACE inhibitors on the growth of mouse liver cancer, thus reporting that perindopril significantly inhibited the growth of liver cancer, probably though its neovascularization inhibiting effect[6)7)] in comparison to the control. It is possible that ACE inhibitors exert a neovascularization inhibiting effect on cancers with a strong tumor vessel proliferation such as liver cancer. To examine the effect of ACE inhibitors on the recurrence of HCC, we retrospec-

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tively investigated recurrence after treatment of HCC in patients who had taken a antihypertensive agent over a long period of time for the treatment of hypertension accompanying HCC.

Subjects and Methods

1. Patients

Of the 318 patients who were diagnosed to have HCC and received initial treatment (percutaneous ethanol injection therapy, hepatic artery embolization therapy and combined use of both therapies) at Fukuoka University Hospital during a 5-year period, 234 patients had a HCC a tumor diameter of less than 5 cm, a hepatic reserve capacity classified as A or B according to the Child' classification and a clinical effectiveness rated as either a complete response (CR) or good partial response (PR). The diagnosis of HCC was made based on abdominal ultrasonography (US), computed tomography (CT) imaging, and/or hepatic arterial angiography, tumor target biopsy. Of them, 32 patients who had been complicated by hyertension and had taken only one kind of antihypertensive agent regularly (mean age 67.6±7.0 years, range 53–80) were thus selected as the subjects. Hypertension was defined as either a systolic pressure consistently at 140 mmHg or higher or a diastolic pressure consistently at 90 mmHg or higher. They included 24 males and 8 females. Of the 32 patients, ten patients of them were taking ACE inhibitor and 22 patients were taking calcium antagonist. The ACE inhibitors administered to ten cases of the ACE inhibitor group were enalapril for five cases, imidapril for three cases and temocapril for two cases. Both antihypertensive agents were continuously administrated throughout the follow-up period. They were divided into the ACE inhibitor group and calcium antagonist group for study of the recurrence rate. Of the remaining 202 patients, 189 patients excepting 13 patients taking antihypertensive agents other than ACE inhibitors or calcium antagonists or more than two antihypertensive agents were designated as the antihypertensive agent non-administration group, and the cumulative recurrence rate of these 189 patients was used as the drug non-administration control (Figure 1).

2. Follow-up of the patients

After the complete initial treatment for HCC, the patients were followed up at the outpatient department. When a new lesion of HCC found by abdominal US or CT during a regular observation, it was defined as recurrence.

3. Statistical analysis

The data are presented as the means±standard deviation. The significance of differences among different groups was determined by Student's t-test. Recurrent curves were constructed according to the Kaplan-Meier method and were compared using the log-rank test.

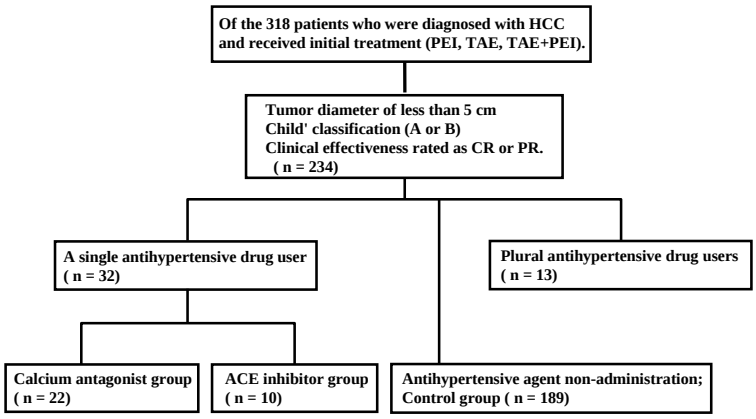

Figure 1. Study flow chart. PEI : percutaneous ethanol injection therapy, TAE : hepatic artery embolization therapy, CR : complete response, PR partial response.

Results

Table 1 shows the clinical features. No significant difference was found in the tumor diameter and number of tumors. Nor was there any significant difference in the liver reserve capacity including alubumin, PT, and total bilirubin. No significant difference in the blood pressure was found between the two groups during the administration of antihypertensive drugs. The systolic blood pressure was significantly higher in the two groups in comparison to the control.

The recurrence rate was 50%, number of days of recurrence 590 in the ACE inhibitor group and 50%, 713 in the calcium antagonist group, but statistically no significant difference was found. The comparison between each with the control did not show any significant difference in comparison to the rate of recurrence (Figure 2).

Complications other than hypertension in the patients taking depressors included diabetes in nine cases, chronic renal failure in three cases, long-standing cerebral infarction in two cases and long-standing cerebral hemorrhage in one case. No serious events due to these diseases were found during the follow-up period. Three patients died during the follow-up. No patient died due to the side effects of the medicine. As for their cause of death, hepatic failure death (decompensation liver

Table 1. Clinical characteristics of two groups.

	ACE inhibitor group	Calcium antagonist group	Control group
Number of patients	10	22	189
Sex (male : female)	8 : 2	16 : 6	114 : 75
Age (yr.)	69.3±6.9	66.8±7.1	67.5±9.1
Treatment (PEI:TAE:TAE+PEI)	4 : 3 : 3	10 : 5 : 7	10 : 5 : 7
SBP (mmHg)	140.8±21.4*	142.9±13.0*	136.7±24.4
DBP (mmHg)	75.6±8.2	82.9±8.1*	72.7±9.4
heart rate (/min)	72.4±8.8	70.7±8.0	68.5±9.5
Tumor size (mm)	26.5±13.0	24.3±0.9	25.8±12.4
Number of tumors	2.0±0.9	1.7±1.0	1.9±0.9
Albumin (g/dl)	4.06±1.11	3.71±0.53	3.86±1.25
Total Bilirubin (mg/dl)	0.70±0.30	0.75±0.28	0.73±0.33
PT (%)	87.0±13.9	81.8±14.4	85.2±15.6
AST (IU/l)	54.0±19.8	69.7±39.1	62.8±26.2
ALT (IU/l)	58.4±30.6	70.9±40.3	61.7±33.0
BUN (mg/dl)	17.5±6.5	16.7±7.3	16.9±8.4
Creatinine (mg/dl)	0.96±0.36	0.86±0.34	0.91±0.58
Follow-up for HCC (years)	1.0−4.8	1.0−5.2	0.5−5.2

ACE : angiotensin converting enzyme ; PEI : percutaneous ethanol injection therapy ; TAE : hepatic artery embolization therapy ; SBP : systolic blood pressure ; DBP : diastolic blood pressure ; PT : prothrombin time ; ICG R15% : indocyanine green clearance teat ; AST : asparate aminotransferase ; ALT : alanine aminotransferase ; BUN : blood urea nitrogen ; NS : not significant. *P<0.05 vs Control group

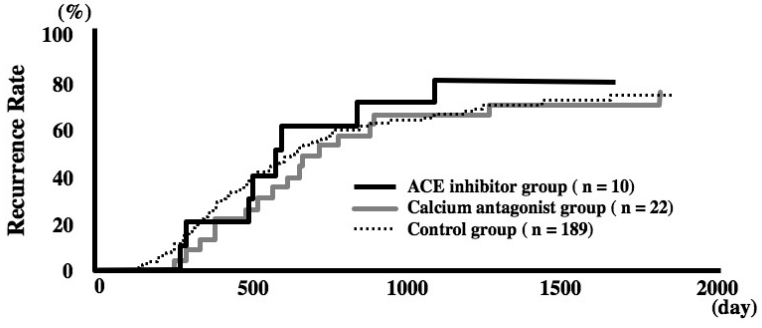

Figure 2. The significant difference was not recognized among three groups.

cirrhosis) was the cause in two cases and tumor death (HCC) was the cause in one case.

Discussion

HCC has a high rate of recurrence two years after treatment in from 40–80% of all cases in comparison to other cancers because of its multicentral growth and intrahepatic metastasis. However, no drugs significantly inhibiting recurrence are yet available.

The long-term administration of ACE inhibitors has been reported to lead to a decrease in the mortality rate of cancer.[5]

Yoshiji *et al*. examined effects of ACE inhibitors on the growth of HCC transplanted to nude mouse, and they concluded that perindopril among the ACE inhibitors significantly inhibited the growth of liver cancer in comparison to the control.[6][7] Furthermore, angiotensin II accelerated the expression of VEGF mRNA and angiotensin II had a neovascularization-promoting effect.[8][9] In addition, neovascularization in diabetic retinopathy has also been reported to be inhibited by the administration of ACE inhibitors.[10][11] Presumably, the production of angiotensin II is inhibited by the administration of ACE inhibitors and, as a result, the neovascularization of tumors is hindered and the growth of tumors is suppressed.

Our research did not demonstrate any significant difference in the recurrence rate of HCC patients in the ACE inhibitor group, calcium antagonist group, and control group. The results of our recurrence rate of HCC were the same as the recurrence rate of HCC of other reports.[1]–[4] The following may be mentioned as a possible reason why no significant difference in the recurrence of cancer was found between the ACE inhibitor group, calcium antagonist group and non-antihypertensive agent administration group in the present study.

Yoshiji *et al*. suggested that the influence of the ACE inhibitor on angiogenesis occurs in a compound-specific manner.[5] VEGF is now widely known to be one of the most potent angiogenic factors, and as a survival factor of tumor. VEGF and its receptor interaction is believed to play a major role in angiogenesis in human tumors. VEGF is regulated by several factors, including AT-II. The ACE inhibitor perindopril has been shown to significantly inhibit tumor growth and angiogenesis along with suppression of the VEGF level. An other possible cause, perindopril which was described in Yoshiji's report, was not investigated in our research. In addition, there is a difference in the quantity of the ACE inhibitor between animal experiments and the clinical dose.

The chymase system is a system by which the production of angiotensin II does not depend on an angiotensin-converting enzyme.[12]–[14]

An angiotensin II receptor antagonist was developed which does not contribute to the chymase system.[15][16]

Based on the above findings, a prospective investigation using these angiotensin II receptor antagonists is thus considered to be required.

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