Transcatheter arterial infusion chemotherapy prior to radiofrequency thermal ablation for single hepatocellular carcinoma reduces the risk of intrahepatic distant recurrence

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Abstract. The aim of the present study was to elucidate the effectiveness of transcatheter arterial infusion chemotherapy (TAI) of the whole liver using an epirubicin-mitomycin-lipiodol emulsion, prior to radiofrequency thermal ablation (RFA), in preventing intrahepatic distant recurrence (IDR) from single hepatocellular carcinoma (HCC). Of the 269 consecutive patients who underwent RFA in our institute for single HCC, a total of 182 patients were analyzed in the present study. The primary endpoint was comparison of the post-RFA IDR-free survival rates in patients treated using TAI with an epirubicin-mitomycin-lipiodol emulsion via the proper hepatic artery (TAI-EML) prior to RFA, and patients that received lipiodol infusion-alone prior to RFA. The secondary endpoints were local tumor progression (LTP) and overall survival (OS). Lipiodol infusion-alone prior to RFA was performed in 88 patients and TAI-EML prior to RFA in 94 patients. The mean tumor size was 2.06 cm (range, 0.9-3.2 cm) in the TAI group and 1.97 cm (range, 0.9-3.3 cm) in the lipiodol-alone group, respectively. The cumulative IDR-free survival rates at 1, 2 and 3 years were 74.0, 50.8 and 34.9%, respectively, in the lipiodol-alone group, and 90.8, 74.8 and 70.0%, respectively, in the TAI group (P<0.001). In terms of the OS, there was a significant difference between these two groups (P=0.048), although there was no significant difference in terms of the LTP (P=0.145). We concluded that TAI-EML prior to RFA appears to be useful in reducing post-RFA IDR and may contribute to improved survival rates.

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Key words: hepatocellular carcinoma, transcatheter arterial infusion chemotherapy, radiofrequency thermal ablation, epirubicin, mitomycin, recurrence

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer; it is the fifth most common malignancy worldwide and the third most common cause of cancer-related mortality (1). Current options for the treatment of HCC include surgical resection, liver transplantation, transcatheter arterial embolization (TAE) or chemoembolization (TACE), transcatheter arterial infusion chemotherapy (TAI), percutaneous ethanol injection therapy (PEIT), percutaneous radiofrequency thermal ablation (RFA) therapy, radioembolization and molecular-targeted drugs such as sorafenib (2-5). However, HCC frequently recurs after treatment, leading to high mortality rates. In 68 to 96% of patients recurrence only occurs at intrahepatic sites (6). Therefore, prevention and effective management of intrahepatic distant recurrence (IDR) are important strategies for improving overall survival after curative treatment of HCC (7).

Interferon treatment for chronic hepatitis C and nucleoside analogue treatment for chronic hepatitis B have been reported as being useful in preventing IDR after curative treatment for HCC (8-10).

The objectives of adjuvant regional chemotherapy are to prevent tumor recurrence from the primary tumor or to reduce the incidence of a second HCC. Compared with systemic chemotherapy, TAI has the advantages of increasing the local concentration of chemotherapeutic agents for killing cancer cells, while causing less damage to healthy liver tissue and reducing systemic side-effects (11). However, to our knowledge, there have been few reports on effective neoadjuvant regional chemotherapy or adjuvant regional chemotherapy for preventing IDR (7,12,13).

In our department, we have routinely performed hepatic arterial infusion chemotherapy using an epirubicin-mitomycin-lipiodol emulsion for HCC when carrying out angiography, since the approval of these chemotherapeutic agents for the treatment of HCC in Japan. However, convincing evidence supporting the effectiveness of TAI with an epirubicin-mitomycin-lipiodol emulsion before RFA in preventing IDR is currently lacking.

The aim of the present study was to elucidate the effectiveness of TAI using an epirubicin-mitomycin-lipiodol emulsion,

administered via the proper hepatic artery to the whole liver (TAI-EML), prior to RFA, in preventing IDR for single HCC.

Materials and methods

Study design. The present study was a single center and retrospective study. Prior to angiography and RFA, written informed consent was obtained from all the patients. The protocols for angiography and RFA were approved by the ethics committee of our department (Fig. 1).

We assessed the electronic medical records of patients registered in our database. The primary endpoint was post-RFA IDR-free survival, and the secondary endpoints were local tumor progression (LTP) and overall survival (OS).

Patients. We performed RFA in 269 consecutive treatment-naive patients diagnosed with solitary and hypervascular HCC in the Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Japan, between January 2004 and October 2010. During the period from January 2004 to April 2005 and from December 2008 to October 2010, we routinely performed TAI-EML prior to RFA. Between May 2005 and October 2008, only lipiodol infusion was performed prior to RFA, as we were using the protocols of several clinical studies that we had participated in. Lipiodol (Lipiodol Ultra-Fluid, Schering Japan, Osaka, Japan) accumulates selectively in tumors when infused intra-arterially (14). Therefore, lipiodol infusion was performed to improve tumor visibility when assessing the effectiveness of RFA using dynamic computed tomography (CT). A representative case is shown in Fig. 2.

Of the 269 patients mentioned above, patients who met the following inclusion criteria were analyzed: a) complete ablation of RFA; and b) no evidence of other malignancies. We excluded patients who had: a) incomplete ablation of RFA; b) interferon treatment for chronic hepatitis C; c) nucleoside analogue treatment for chronic hepatitis B; and d) only segmental TAI before RFA due to the decision of attending physicians (Fig. 1). Complete ablation was defined as no apparent residual tumors on dynamic CT performed within 7 days after RFA and was determined by three radiologists (not blinded) experienced in liver imaging. In patients with incomplete RFA, TACE was performed after RFA.

Diagnosis of HCC. HCC was diagnosed using abdominal ultrasound and dynamic CT scans (hyperattenuation during the arterial phase in all or some part of the tumor and hypoattenuation in the portal-venous phase) and/or magnetic resonance imaging (MRI), mainly based on the recommendations of the American Association for the Study of Liver Diseases (15). Arterial and portal phase dynamic CT images were obtained at approximately 30 and 120 sec, respectively, after the injection of the contrast material. In our department, abdominal angiography combined with CT (angio-CT) assistance was performed on all patients before RFA; CT during hepatic arteriography (CTHA) was performed with the catheter tip in the proper hepatic artery and CT during arterial-portography (CTAP) was performed with the catheter tip in the superior mesenteric artery, as Yamasaki *et al* reported that this technique was useful for detecting small satellite nodules (16). Then, we confirmed the presence of single and hypervascular HCC with no vascular invasion using CTHA and CTAP. Immediately after evaluation using angio-CT, TAI-EML or lipiodol infusion-alone via the proper hepatic artery was performed in the same session.

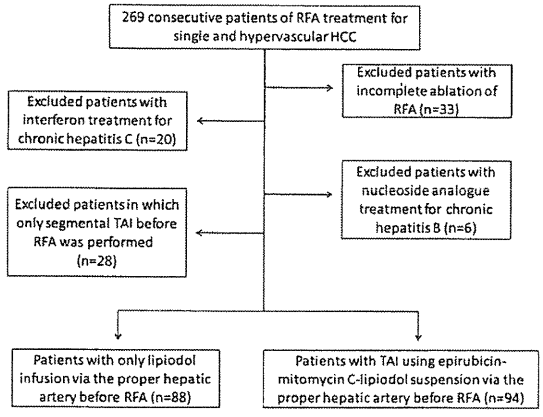

Figure 1. Study profile.

Treatment procedure

TAI. A catheter was introduced into the proper hepatic artery using the Seldinger technique. This was followed by an intra-arterial infusion via the proper hepatic artery according to tumor size and liver function, of an emulsion containing epirubicin (mean dose, 28.2 mg; range, 10-40 mg), mitomycin (mean dose, 6.2 mg; range, 4-10 mg) and lipiodol (mean dose, 2.1 ml; range, 1-3 ml) in the TAI group and of lipiodol alone (mean dose, 1.9 ml; range, 1-3 ml) in the lipiodol-alone group, respectively. When patients had poor liver function, the dosage of the anticancer agents and lipiodol were reduced.

Epirubicin-mitomycin-lipiodol emulsion. Epirubicin (Farmorubicin; Kyowa Hakko Kirin Company, Ltd., Tokyo, Japan) is an anthracycline-based anticancer drug and is the 4'-epimer of doxorubicin. Epirubicin, as well as doxorubicin, binds to the deoxyribonucleic acid (DNA) in tumor cells, leading to suppression of DNA synthesis (17). Mitomycin (Mitomycin C; Kyowa Hakko Kirin Company, Ltd., Tokyo, Japan) is changed into activated metabolites by various enzymes, and these block DNA replication in tumor cells leading to antitumor effects (18). Due to the fact that epirubicin easily undergoes glucuronidation, its toxicity is milder than that of doxorubicin. In 1986, the Japan Epirubicin Study Group for Hepatocellular Carcinoma reported that in 53 HCC patients who had received TAI with epirubicin, eight of the patients had an objective response. A retrospective comparison of this result with that of patients that were treated using TAI with doxorubicin demonstrated that epirubicin was more effective than doxorubicin in terms of survival rate (17). Since that time, epirubicin has been conventionally used in TAI for HCC in Japan, and additional clinical trials have been performed in several faculties. Epirubicin alone or in combination with other chemotherapeutic agents such as mitomycin C has been used in TAI for HCC in Asian countries, including Japan (17).

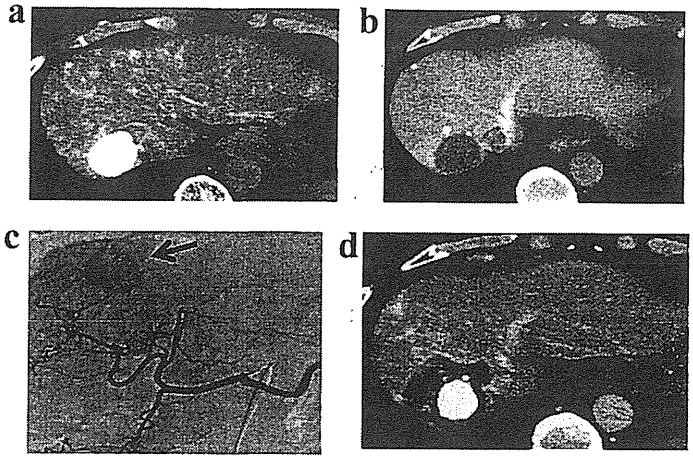

Figure 2. Representative case. (a) CT during hepatic arteriography (CTHA). Contrast material was injected via the proper hepatic artery; an enhanced region can be seen in the hepatocellular carcinoma (HCC) and is approximately 2.7 cm in size and located at segment 7. (b) CT during arterial-portgraphy (CTAP). Contrast material was injected via the superior mesenteric artery; a defect region is evident in the HCC and is approximately 2.7 cm in size located at segment 7. (c) Digital subtraction angiography (DSA). Contrast material was injected via the proper hepatic artery. The tumor stain can be seen in the HCC located at segment 7 (arrow). (d) Dynamic CT findings in delayed phase after radiofrequency thermal ablation (RFA) with lipiodol infusion via the proper hepatic artery. A dense accumulation of lipiodol is apparent in the tumor identifying the exact location of the tumor. An ablative margin around the entire tumor was obtained in this case.

Considering this background, we have conventionally performed TAI for HCC in our department with an epirubicin-mitomycin-lipiodol emulsion.

RFA. In all patients, the first session of RFA was performed within 7 days after angiography. We routinely used a cool-tip needle (Radionics Corp., Burlington, MA, USA) while performing RFA. Under local anesthesia, using the intercostal or subcostal approach, an electrode was inserted under real-time ultrasound guidance. The initial treatment was planned with one ablation for tumors of <2 cm in diameter, and two or more ablations with the overlapping technique for tumors of ≥2 cm in diameter. When tumor ablation was complete, thermal ablation was performed along the needle track. We did not use the coaxial technique. All patients were carefully observed for treatment-related complications. The procedures were all conducted under ultrasound guidance by one of five operators who had at least 3 years of experience in performing RFA.

Follow-up. Follow-up after RFA consisted of monthly blood tests and monitoring of tumor markers, including α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), which were measured using a chemiluminescent enzyme immunoassay (Lumipulse PIVKAII Eisai, Tokyo, Japan). Abdominal ultrasonography and dynamic CT scans were obtained every 3-4 months following RFA.

Definition of IDR and LTP. We defined IDR as the recurrence of a new lesion (excluding extrahepatic metastasis) at a distant site from the ablation zone detected using a dynamic CT scan. When a new lesion appeared in the same segment as the original tumor, we defined it as IDR if it was not adjacent to the ablation zone. We defined local tumor progression (LTP) as the presence of a hypervascular nodule adjacent to the ablation zone after RFA revealed using a dynamic CT scan (19). Recurrence that was distant from the ablation zone in the same segment was not included in the definition of LTP. IDR and LTP were determined by the same three radiologists (not blinded) as described above.

Statistical analysis. Intercomparison of the lipiodol-alone group and the TAI group was performed using the unpaired t-test or Fisher's exact test. Data were expressed as the mean ± standard deviation and were analyzed using univariate and multivariate analyses. The cumulative post-RFA IDR-free survival rate, the cumulative LTP rate and the cumulative OS rate were calculated using the Kaplan-Meier method, and tested using the log-rank test. Regarding factors contributing to IDR, the Cox proportional hazard model was used for multivariate analyses of factors that were considered significant in univariate analysis. These statistical methods were used to estimate the interval from RFA treatment. Data were analyzed using SPSS software, version 9.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows. P-values <0.05 were considered to indicate statistically significant differences.

Results

Patients and recurrence. In 94 of the 182 patients analyzed in the present study, between January 2004 and April 2005 and between December 2008 and October 2010, TAI-EML was performed prior to RFA. Over the period from May 2005 to October 2008, infusion involving lipiodol-alone via the proper hepatic artery was performed prior to RFA in 88 patients.

The baseline characteristics of the two groups are shown in Table I. The mean tumor size was 2.06 cm (range, 0.9-3.2 cm)

Table I. Baseline characteristics of patients in the TAI and lipiodol-alone groups.

	Lipiodol-alone group (n=88)	TAI group (n=94)	P-value
Gender (male/female), n	58/30	56/38	0.444[a]
Age (mean ± SD)	69.6±9.8	69.3±8.1	0.819[b]
Etiology of liver disease, n B/C/non B, non C	2/70/16	4/80/10	0.229[a]
Child-Pugh classification, n Child-A/Child-B/Child-C	77/8/3	80/13/1	0.358[a]
Diabetes Mellitus (yes/no), n	28/60	32/62	0.755[a]
Body mass index (kg/m^2) (mean ± SD)	23.3±3.6	23.1±3.5	0.764[b]
Total bilirubin (mg/dl) (mean ± SD)	0.94±0.56	0.95±0.53	0.859[b]
Albumin (g/dl) (mean ± SD)	3.83±0.52	3.83±0.53	0.988[b]
Platelet (x10^4/μl) (mean ± SD)	10.6±4.7	11.4±4.9	0.247[b]
Prothrombin time (%) (mean ± SD)	87.2±15.6	87.4±16.3	0.922[b]
AST (IU/l) (mean ± SD)	61.0±37.2	53.9±31.2	0.164[b]
ALT (IU/l) (mean ± SD)	58.4±64.7	54.9±28.9	0.157[b]
AFP (ng/ml) (mean ± SD)	120.7±530.4	111.2±335.9	0.885[b]
DCP (mAU/ml) (mean ± SD)	215.0±1114.5	288.0±1559.4	0.718[b]
Tumor size (cm) (mean ± SD)	1.97±0.63	2.06±0.66	0.397[b]

SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; TAI, transcatheter arterial infusion chemotherapy; [a]Fisher's exact test; [b]unpaired t-test.

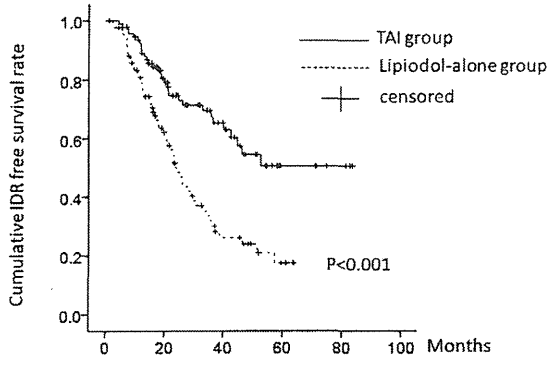

Figure 3. Cumulative intrahepatic distant recurrence (IDR)-free survival rates in the lipiodol alone and TAI groups. The cumulative IDR-free survival rates at 1, 2 and 3 years were 74.0, 50.8 and 34.9%, respectively, in the lipiodol-alone group. The cumulative IDR-free survival rates at 1, 2 and 3 years were 90.8, 74.8 and 70.0%, respectively, in the TAI group. There was a significant difference in the IDR-free survival rates between the two groups (P<0.001).

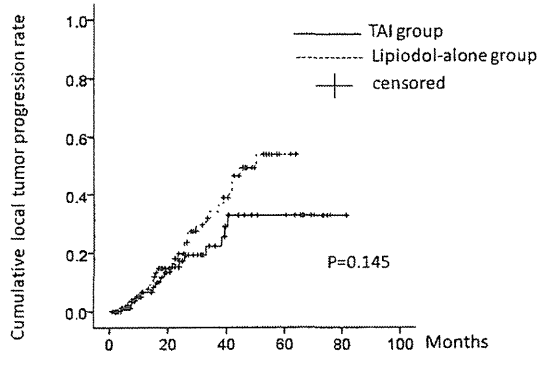

Figure 4. Cumulative local tumor progression (LTP) rate. The 1-, 2- and 3-year LTP rates were: 8.4, 17.4 and 22.2%, respectively, in the TAI group and 8.6, 19.6 and 34.9%, respectively, in the lipiodol-alone group. In terms of the LTP rate, there was no significant difference between these two groups (P=0.145).

in the TAI group and 1.97 cm (range, 0.9-3.3 cm) in the lipiodol-alone group, respectively. There were no significant differences between the two groups in terms of baseline characteristics. At a median follow-up interval of 36.4 months (range, 6.2-83.6 months), 55 (62.5%) of the 88 patients in the lipiodol-alone group and 31 (33.0%) of the 94 patients in the TAI group had IDR. The cumulative post-RFA IDR-free survival rates at 1, 2 and 3 years were 74.0, 50.8 and 34.9%, respectively, in the lipiodol-alone group, and 90.8, 74.8 and 70.0%, respectively, in the TAI group (P<0.001). There was a significant difference in the post-RFA IDR-free survival rate between the two groups (P<0.001) (Fig. 3).

Univariate and multivariate analysis. Using univariate analysis, age ≥70 years (P=0.046), platelet count ≥10x10^4/μl (P<0.001), des-γ-carboxy prothrombin level (DCP ≥100 mAU/ml) (P=0.030) and TAI-EML before RFA (P<0.001) were found to be significant factors contributing to IDR (Table II). In the multivariate analyses involving the four factors that were found to be significant in the univariate analysis, hazard ratios (HRs), 95% confidence interval and P-values are detailed in

Table II. Univariate analysis of parameters contributing to post-RFA IDR.

	N	P-value[a]
Gender (male) (yes/no)	114/68	0.763
Age >70 years (yes/no)	102/80	0.046
Child-Pugh classification (Child-Pugh A) (yes/no)	157/25	0.382
Diabetes Mellitus (yes/no)	60/122	0.243
Body mass index (>25 kg/m^2) (yes/no)	51/131	0.560
Total bilirubin (>1.0 mg/dl) (yes/no)	64/118	0.190
Albumin (>3.5 g/dl) (yes/no)	142/40	0.710
Platelet (>10x10^4/μl) (yes/no)	101/81	<0.001
Prothrombin time (>80%) (yes/no)	124/58	0.211
AST (>60 IU/l) (yes/no)	65/117	0.277
ALT (>60 IU/l) (yes/no)	51/131	0.399
AFP (>100 ng/ml) (yes/no)	30/152	0.201
DCP (>100 mAU/ml) (yes/no)	36/146	0.030
Tumor size (>2.0 cm) (yes/no)	92/90	0.284
TAI to the whole liver (yes/no)	94/88	<0.001

RFA, radiofrequency ablation; IDR, intrahepatic distant recurrence; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; TAI, transcatheter arterial infusion chmenotherapy; [a]Kaplan-Meier method.

Table III. Multivariate analysis contributing to post-RFA IDR.

	Hazard ratio	95% CI	P-value[a]
Age >70			
Yes	1.000		
No	0.673	0.435-1.042	0.076
Platelet >10x10^4/μl			
Yes	1.000		
No	2.279	1.469-3.536	<0.001
DCP >100 mAU/ml			
Yes	1.578	0.830-3.001	0.164
No	1.000		
TAI before RFA			
Yes	1.000		
No	2.260	1.448-3.528	<0.001

CI, confidence interval. [a]Cox proportional hazard model. DCP, des-γ-carboxy prothrombin; IDR, intrahepatic distant recurrence; RFA, radiofrequency thermal ablation; TAI, transcatheter arterial infusion chemotherapy.

Table III. A platelet count of ≥10x10^4/μl and TAI-EML were found to be significant independent factors linked to IDR.

LTP. During the observation period, 16 patients (17.0%) in the TAI group and 28 patients (31.8%) in the lipiodol-alone group, respectively, had LTP. The 1-, 2- and 3-year LTP rates were: 8.4, 17.4 and 22.2%, respectively, in the TAI group and 8.6, 19.6 and 34.9%, respectively, in the lipiodol-alone group. In terms of the LTP rate, there was no significant difference between these two groups (P=0.145) (Fig. 4).

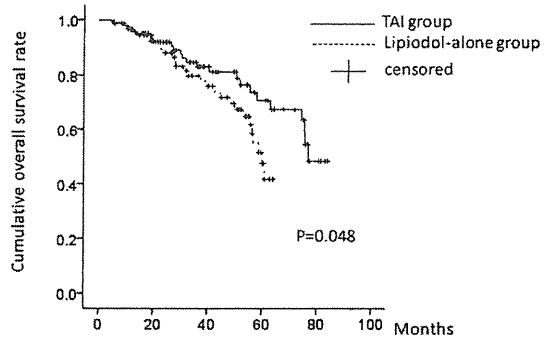

Figure 5. Cumulative overall survival (OS) rate. The 1-, 3- and 5-year OS rates were: 96.0, 83.7 and 71.1%, respectively, in the TAI group and 96.0, 79.6 and 51.0%, respectively, in the lipiodol-alone group. In terms of the OS rate, there was a significant difference between the two groups (P=0.048).

OS. During the observation period, 23 patients (24.5%) in the TAI group and 30 patients (34.1%) in the lipiodol-alone group, respectively, succumbed to the disease. Four patients (4.3%) in the TAI group and six patients (6.8%) in the lipiodol-alone group, respectively, were lost to follow-up. The causes of mortality were HCC recurrence (17 patients), liver failure (four patients) and miscellaneous causes (two patients) in the TAI group, and HCC recurrence (23 patients), liver failure (four patients) and miscellaneous causes (three patients) in the lipiodol-alone group, respectively. The 1-, 3- and 5-year OS rates were: 96.0, 83.7 and 71.1%, respectively, in the TAI group and 96.0, 79.6 and 51.0%, respectively, in the lipiodol-alone group. In terms of the OS rate, there was a significant difference between these two groups (P=0.048) (Fig. 5).

TAI adverse events. Patients in the TAI group experienced transient fever, abdominal pain, appetite loss, nausea and elevation of liver enzymes after TAI. However, these side-effects were all grade 1 (as determined using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) (20). Side-effects improved within 3 or 4 days folowing TAI. In the lipiodol-alone group, no side-effects were observed.

Complications associated with RFA. In terms of complications associated with RFA itself, pneumothorax in one patient, biloma in one patient and intra-abdominal bleeding in one patient in the TAI group, and biloma in one patient, refractory ascites in one patient and retroperitoneal bleeding in one patient in the lipiodol-alone group were observed. All patients with complications related to RFA improved during the same hospitalization period. However, one patient in the TAI group required re-admission due to biloma and improved after percutaneous drainage. There were no needle tract implantations and there were no mortalities due to RFA related complications.

Discussion

HCC is suitable for treatment with regional chemotherapy as it has a tendency to stay in the liver until it is at an advanced stage, with extrahepatic metastasis generally occurring late. This suggests that an effective regional chemotherapy would have a great impact on the course of HCC (21). The rationale for regional chemotherapy stems from the difference in the dual blood inflow supply via the portal vein and the hepatic artery between HCC and nontumorous liver. In hypervascular HCC, the hepatic artery generally becomes the only vessel supplying blood to the tumor. Therefore, the hepatic artery is used as a roadway to treat the tumor, whereas the non-tumorous liver is least affected since the portal vein is responsible for supplying most of its blood (6,22). Several clinical trials related to regional chemotherapy have been performed with the aim of reducing the incidence of IDR (6,7,12,13,23,24). However, to our knowledge, there have been few reports on neoadjuvant regional chemotherapy or adjuvant regional chemotherapy that was effective in preventing IDR, either prior to or following curative treatment of HCC (7,12,13).

In contrast to TAI with platinum agents such as cisplatin, TAI with an epirubicin-mitomycin-lipiodol emulsion generally does not cause renal toxicity or a hypersensitivity reaction (17,25). In fact, in the present study, there were no serious complications due to TAI-EML. In all patients, RFA was performed safely within 7 days following TAI. These results suggest that TAI-EML is a safe procedure in terms of adverse effects.

Using univariate analysis, age ≥70 years, platelet count ≥$10x10^4/\mu l$, DCP ≥100 mAU/ml and TAI-EML were found to be significant factors contributing to IDR. Asahina *et al* (26) reported that aging has become one of the most important risk factors for HCC, and Kubo *et al* (27) reported that the platelet count was well correlated with hepatic fibrosis and liver carcinogenesis. Findings in these two studies were similar to our findings using univariate analysis. In the present study, 36 cases (19.8%) had a DCP value of ≥100 mAU/ml. It has also been reported (28) that high DCP levels reflect the aggressiveness and progression of HCC tumors and that the DCP level is a predictor of microvascular invasion. These findings seem to correlate with our results. However, using multivariate analysis, the platelet count ≥$10x10^4/\mu l$ and TAI-EML before RFA were found to be significant factors linked to IDR. Moreover, in terms of the OS rate, there was a significant difference between these two groups in the present study. These results suggest that suppression of the progression of hepatic fibrosis as well as TAI-EML before RFA appears useful in preventing post-RFA recurrence and might contribute to improved survival rates.

It is generally believed that recurrences after curative treatment for HCC in the early post-treatment period arise, not because of incomplete treatment of the primary tumor but because of pre-existing microscopic tumor foci that are not detected by imaging modalities; in addition, recurrence can be caused by malignant cells that have been disseminated during treatment (29). TAI-EML before RFA may prevent an increase in size of pre-existing microscopic tumor foci.

In terms of LTP, there was no significant difference in the two groups. In reducing LPT after RFA, obtaining sufficient ablative margin is considered to be essential (30).

The present study had several limitations: i) it was a retrospective study carried out over a long period of 6 years; ii) histological examination of each target HCC was not performed, although it has been reported that pathological and biological factors have been found to be useful and have helped guide clinicians in the management of HCC patients (31); iii) the median observation period in the present study was relatively short compared with previous studies; iv) patients with incomplete ablation of RFA were excluded in the present study, leading to a bias; v) there were some patients lost to follow-up, leading to the possibility of under-estimating the true recurrence and survival rates. Therefore, a prospective and randomized study of whole liver treatment with an epirubicin-mitomycin-lipiodol emulsion is required in the future. However, our findings demonstrate a significant IDR preventive effect in the TAI group, suggesting the usefulness of whole liver treatment with TAI using an epirubicin-mitomycin-lipiodol emulsion.

In conclusion, RFA and sequential TAI-EML may contribute to a longer recurrence-free period and overall survival.

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Comparison of the efficacy of transcatheter arterial chemoembolization and sorafenib for advanced hepatocellular carcinoma

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Abstract. The aim of the present study was to compare overall survival between stage IVA or stage IVB hepatocellular carcinoma (HCC) patients who received transcatheter arterial chemoembolization (TACE) and those who were treated with sorafenib. This retrospective comparative study included 55 patients with stage IVA or IVB HCC in whom TACE was performed as an initial treatment (the TACE group) and 56 patients with stage IVA or IVB HCC to whom sorafenib was administered (the sorafenib group). We compared the overall survival between these two groups. In the TACE group, there were 46 stage IVA HCC patients and 9 stage IVB HCC patients. In the sorafenib group, there were 26 stage IVA HCC patients and 30 stage IVB HCC patients. Median overall survival times were 6.6 months in the TACE group and 9.2 months in the sorafenib group. The 1- and 2-year overall survival rates were 34.4 and 14.2%, respectively, in the TACE group and 34.0 and 6.7%, respectively, in the sorafenib group. In terms of overall survival, there was no significant difference between the two groups (P=0.814). In subgroup analyses, according to HCC stage [stage IVA (P=0.266) or stage IVB (P=0.183)] and Child-Pugh classification [Child-Pugh A (P=0.915) or Child-Pugh B (P=0.676)], there were also no significant differences between the two groups. In conclusion, our study results suggest that TACE could serve as a first-line treatment for stage IV HCC patients as well as sorafenib therapy.

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Key words: hepatocellular carcinoma, transcatheter arterial chemoembolization, sorafenib, survival, outcome

Introduction

Hepatocellular carcinoma (HCC) is a problem worldwide, particularly in Asian countries (1-3). Unlike most solid cancers, the incidence and mortality rates for HCC are projected to increase substantially in many countries over the next 20 years, mostly as a result of infections with hepatitis C and hepatitis B viruses (4). It has become possible to identify a group of patients with chronic liver disease who are at a high risk of developing HCC. In addition, improvements in diagnostic imaging have allowed early diagnosis of HCC. However, the majority of HCC patients are first seen when the disease has reached an advanced stage at which curative treatment is no longer possible (4).

Since HCC is considered to be chemoresistant in general, results of systemic chemotherapy have previously been disappointing (5). Sorafenib (Nexavar, Bayer Healthcare Pharmaceuticals), a multi-kinase inhibitor that blocks tumor growth and cell proliferation, was the first systemic chemotherapeutic agent found to improve the survival time of patients with advanced HCC in the SHARP and Asian Pacific trials (6,7). Sorafenib has opened a novel era for the treatment of advanced HCC. However, it is associated with a low tumor response rate, minimal survival advantage and high rates of adverse events (6,7).

Transcatheter arterial chemoembolization (TACE) is a procedure whereby an embolizing agent is injected into the hepatic artery to deprive the tumor of its major nutrient source via embolization of the nutrient artery, resulting in ischemic necrosis of the tumor with minimization of systemic side effects. It has become the most popular palliative treatment for patients with unresectable HCC (8-10). Patients with well preserved liver function and multi-nodular HCC without vascular invasion appear to be the best candidates for TACE (8-10). However, TACE is no longer considered to be contraindicated in advanced HCC with portal vein tumor thrombus (PVTT) (11,12), and even in advanced HCC patients with extrahepatic metastasis, in cases in which extrahepatic spread is minimal and local control of liver tumors is considered more important, TACE is useful and may obtain survival

benefits and has often been used in these cases in Japan (5,13). However, the long-term outcomes are less favorable in general for advanced HCCs treated with TACE, since the devascularization effect induced by TACE is transient, resulting in tumor progression (14).

Recently, concurrent or sequential treatment methods of advanced HCC with TACE and sorafenib with a manageable safety profile and a possibility of promising efficacy have been reported (15,16). However, regarding comparison of survival outcomes of advanced HCC patients treated with TACE and those treated with sorafenib, there have been no reliable data to the best of our knowledge to date.

The present study aimed to compare overall survival between stage IVA or IVB HCC patients who received TACE and those who were treated with sorafenib.

Patients and methods

Patients. This retrospective comparative study included 55 patients with stage IVA or IVB HCC in whom TACE was performed as an initial treatment (the TACE group) between April 2004 and November 2011 at the department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Japan and 56 patients with stage IVA or IVB HCC in whom sorafenib was administered (the sorafenib group) between June 2009 and October 2011 at our department. Since the aim of the present study was to compare clinical outcomes between stage IV HCC patients treated with TACE and those treated with sorafenib, 6 patients in whom TACE was performed as an initial treatment and thereafter sorafenib treatment was started were excluded in the present study. None of the TACE group patients received systemic chemotherapy and locoregional therapy other than TACE during the follow-up period. None of the sorafenib group patients received previous systemic chemotherapy. After patients were provided with sufficient information regarding TACE and sorafenib treatment, they themselves decided whether they were treated with TACE or sorafenib. Written informed consent was obtained from all patients prior to each treatment and this study protocol complied with all provisions of the Declaration of Helsinki.

Diagnosis of HCC. HCC was diagnosed using abdominal ultrasound and dynamic computed tomography (CT) scans (hyperattenuation during the arterial phase in all or some part of the tumor and hypoattenuation in the portal-venous phase), mainly based on the recommendations of the American Association for the Study of Liver Diseases (17). The presence of vascular invasion of the tumor was confirmed with the demonstration of a low-attenuation intraluminal mass expanding the portal vein, the bile duct, or the hepatic vein and/or filling defects in these vascular sites at dynamic CT. Arterial and portal phase dynamic CT images were obtained at approximately 30 and 120 sec, respectively, after injecting contrast material. Abdominal CT, chest CT, bone scintigraphy, brain CT and/or brain magnetic resonance imaging were performed prior to treatment in all stage IVB HCC patients. Diagnosis of stage IVB HCC was determined using these imaging modalities. Histopathological examination for metastasis was not performed. All eligible patients in the present study had bidimensionally measurable, inoperable HCC, no prior systemic treatments for HCC, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a Child-Pugh classification of either A or B.

TACE procedure. TACE for HCC was performed in conformity with Japanese guidelines for this therapy, comprising catheterization via the femoral artery with super-selective cannulation to the hepatic artery feeding the target HCC (18). Farmorubicin (epirubicin hydrochloride; Pfizer, New York, NY, USA) was infused at 20-60 mg, mitomycin (mitomycin C; Kyowa Hakko, Tokyo, Japan) was infused at 4-14 mg, and Lipiodol (iodine addition products of ethyl esters of fatty acids obtained from poppy seed oil; Mitsui, Japan) was also injected at 2-15 ml according to the tumor size and tumor number. This was followed by embolization with gelatin (Spongel; Yamanouchi, Japan), which was injected slowly to prevent reflux into untreated segments. The sites of injection of the embolizing agents were segmental or subsegmental in all patients.

In the TACE group, after the initial TACE, another session of TACE was performed every 4-12 weeks until one of the following end points were reached: i) technical impossibility in performing TACE; ii) complete devascularization of the target HCC; iii) development of contraindications to TACE such as liver failure.

Sorafenib dose and treatment. Initiated sorafenib dose was determined considering factors such as patient's body weight, performance status, and liver function. In all patients with Child-Pugh B, the initiated sorafenib dose was 200 mg twice a day (b.i.d.). Sorafenib treatment continued until one of the following criteria was met: disease progression, unacceptable drug-related toxicities or patient's wish for discontinuation.

Evaluation of treatment efficacy. Tumor response was assessed at 8-12 weeks according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria using dynamic CT scans. The change in viable perfused tumor volume of the targeted lesions as measured on the arterial phase imaging before and after treatment was evaluated (19).

Follow-up. In the TACE group, follow-up consisted of monthly blood tests and monitoring of tumor markers. Dynamic CT scans were obtained every 8-12 weeks during the follow-up period. No patients were lost to follow-up in the TACE group. In the sorafenib group, follow-up consisted of weekly blood tests for the purpose of detecting adverse events and monitoring of tumor markers. Dynamic CT scans were obtained every 8-12 weeks during the follow-up period. No patients were lost to follow-up in the sorafenib group.

Statistical analysis. The primary end point was overall survival. It was calculated from the date of first diagnosis with stage IVA or stage IVB HCC using imaging modalities until death from any cause or the last follow-up. Differences between the two groups were analyzed using the unpaired t-test for continuous variables, and the categorical variables were analyzed using the Fisher's exact test. The overall survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. All statistical tests were two-sided. All data

Table I. Baseline characteristics between the TACE group and the sorafenib group.

	TACE group (n=55)	Sorafenib group (n=56)	P-value
Gender (M/F)	42/13	46/10	0.490[a]
Age (years)	67.9±10.0	69.1±12.0	0.563[b]
Etiology of liver disease B/C/B,C/non-B, non-C	7/29/4/15	9/29/1/17	0.575[a]
Child-Pugh classification Child-Pugh A/Child-Pugh B	35/20	42/14	0.221[a]
HCC stage Stage IVA/stage IVB	46/9	26/30	<0.001[a]
Maximum tumor size (cm)	7.6±3.1	6.3±4.4	0.087[b]
Total-bilirubin (mg/dl)	1.03±0.69	0.91±0.50	0.311[b]
Serum albumin (g/dl)	3.51±0.56	3.66±0.49	0.120[b]
Platelets ($x10^4/mm^3$)	16.1±7.7	15.3±8.2	0.595[b]
ALT (IU/l)	66.5±86.8	45.7±39.7	0.106[b]
Prothrombin time (%)	85.8±17.0	82.7±12.4	0.268[b]
AFP (ng/ml)	25,223.4±96,684.3	17,945.7±92,746.3	0.674[b]
PIVKAII (mAU/ml)	50,535.4±83,206.0	28,613.6±117,254.6	0.259[b]
Body mass index (kg/m^2)	22.4±3.3	22.2±4.1	0.756[b]

Data are expressed as the number of patients or the mean ± standard deviation. TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; AFP, α-fetoprotein; PIVKAII, protein-induced vitamin K absence or antagonist II. [a]Fisher's exact test; [b]Student's t-test. B, hepatitis B virus; C, hepatitis C virus.

were analyzed using SPSS software, version 9.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows. Data are expressed as means ± standard deviation (SD). Values of $P<0.05$ were considered to indicate statistical significance.

Results

Baseline characteristics. Baseline characteristics between the TACE group and the sorafenib group are shown in Table I. There were 55 patients in the TACE group and 56 in the sorafenib group. In the TACE group, there were 46 stage IVA HCC patients and 9 stage IVB HCC patients, respectively. In the sorafenib group, there were 26 stage IVA HCC patients and 30 stage IVB HCC patients, respectively. Fifty-one patients (91.1%) in the sorafenib group had received previous locoregional therapies such as percutaneous thermal ablation, percutaneous ethanol injection therapy or transcatheter arterial infusion chemotherapy without embolization, and all patients in the sorafenib group received at least one dose of sorafenib. In terms of HCC stage, there was a significant difference between the two groups ($P<0.001$). However, in terms of gender, age, etiology of liver disease, maximum tumor size, Child-Pugh classification, and laboratory data including tumor markers and body mass index, there were no significant differences between these two groups.

Overall survival. Median overall survival times were 6.6 months in the TACE group and 9.2 months in the sorafenib group. The 1- and 2-year overall survival rates were 34.4 and 14.2%, respectively, in the TACE group and 34.0 and 6.7%, respectively, in the sorafenib group. In terms of overall survival, there was no significant difference between the two groups ($P=0.814$) (Fig. 1).

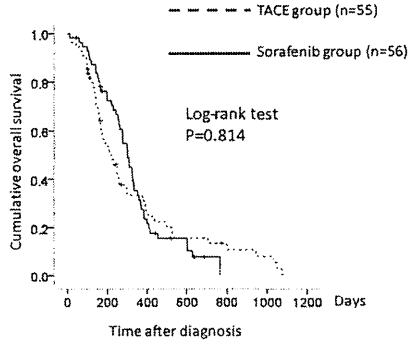

Figure 1. Cumulative overall survival between the transcatheter arterial chemoembolization (TACE) group and the sorafenib group. The 1- and 2-year overall survival rates were 34.4 and 14.2%, respectively, in the TACE group and 34.0 and 6.7%, respectively, in the sorafenib group. In terms of overall survival, there was no significant difference between the two groups ($P=0.814$).

Subgroup analyses

Comparison between the TACE and sorafenib group patients with stage IVA HCC. There were 46 patients in the TACE

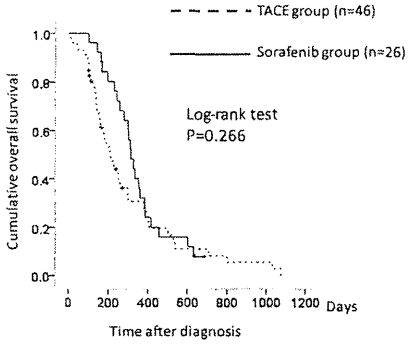

Figure 2. Cumulative overall survival between the transcatheter arterial chemoembolization (TACE) group patients with stage IVA hepatocellular carcinoma (HCC) (n=46) and the sorafenib group patients with stage IVA HCC (n=26). The 1-year overall survival rates were 30.6% in the TACE group and 32.8% in the sorafenib group, respectively. In terms of overall survival, there was no significant difference between the two groups (P=0.266).

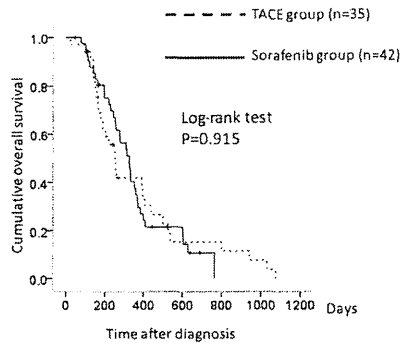

Figure 4. Cumulative overall survival between the transcatheter arterial chemoembolization (TACE) group patients with Child-Pugh A (n=35) and the sorafenib group patients with Child-Pugh A (n=42). The 1-year overall survival rates were 41.1% in the TACE group and 30.4% in the sorafenib group. In terms of overall survival, there was no significant difference between the two groups (P=0.915).

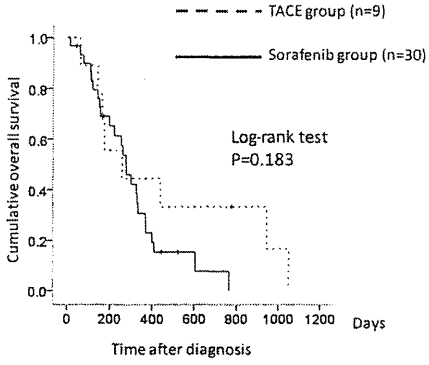

Figure 3. Cumulative overall survival between the transcatheter arterial chemoembolization (TACE) group patients with stage IVB hepatocellular carcinoma (HCC) (n=9) and the sorafenib group patients with stage IVA HCC (n=30). The 1-year overall survival rates were 43.5% in the TACE group and 30.2% in the sorafenib group. In terms of overall survival, there was no significant difference between the two groups (P=0.183).

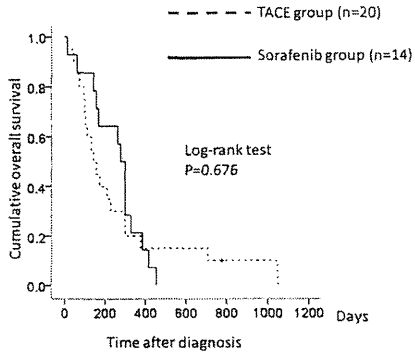

Figure 5. Cumulative overall survival between the transcatheter arterial chemoembolization (TACE) group patients with Child-Pugh B (n=20) and the sorafenib group patients with Child-Pugh A (n=14). The 1-year overall survival rates were 20.0% in the TACE group and 21.4% in the sorafenib group, respectively. In terms of overall survival, there was no significant difference between the two groups (P=0.676).

group with stage IVA HCC and 26 in the sorafenib group. The 1-year overall survival rates were 30.6% in the TACE group and 32.8% in the sorafenib group. In terms of overall survival, there was no significant difference between the two groups (P=0.266) (Fig. 2).

Comparison between the TACE and sorafenib group patients with stage IVB HCC. There were 9 patients in the TACE group with stage IVB HCC and 30 in the sorafenib group. The 1-year overall survival rates were 43.5% in the TACE group and 30.2% in the sorafenib group. In terms of overall survival, there was no significant difference between the two groups (P=0.183) (Fig. 3).

Comparison between the TACE and sorafenib group patients with Child-Pugh A. There were 35 patients in the TACE group with Child-Pugh A and 42 in the sorafenib group. The 1-year overall survival rates were 41.1% in the TACE group and 30.4% in the sorafenib group. In terms of overall survival, there was no significant difference between the two groups (P=0.915) (Fig. 4).

Comparison between the TACE and sorafenib group patients with Child-Pugh B. There were 20 patients in the TACE group with Child-Pugh B and 14 in the sorafenib group. The 1-year overall survival rates were 20.0% in the TACE group and 21.4% in the sorafenib group. In terms of overall survival, there was no significant difference between the two groups (P=0.676) (Fig. 5).

Outcomes in the TACE group. During the follow-up period, a mean of 3.0 (range, 1-9) sessions of TACE were performed in the TACE group. Eighteen patients (32.7%) received 1 session and 37 (67.3%) received more than 1 session of TACE. Partial response (PR) was obtained in 10 patients (18.2%). Stable disease (SD) was observed in 31 patients (56.4%). Progressive disease (PD) was observed in 14 patients (25.5%). The objec-

tive response and disease control rates in the TACE group were 18.2 and 74.5%, respectively.

Adverse events related to TACE. The majority of patients suffered self-limited post-embolization syndrome consisting of low-grade fever, appetite loss, abdominal pain, nausea or mild vomiting, which were effectively controlled and improved within a few days. During the follow-up period, 23 clinical adverse events with grade 3 or higher were observed in the TACE group as determined with National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (20). The details were as follows: appetite loss in 7 patients (12.7%), hepatotoxicity in 6 patients (10.9%), general fatigue in 7 patients (12.7%) and high grade fever in 3 patients (5.5%), respectively. All improved during hospitalization and no patients died of TACE-related adverse events.

Outcomes in the sorafenib group. In the sorafenib group, the median interval between first diagnosis date of stage IVA or IVB HCC and initiation date of sorafenib treatment was 40 days (range, 1-203 days). Median duration of sorafenib therapy was 73 days (range, 4-377 days) for all patients treated with sorafenib. In 42 patients with Child-Pugh A, median duration of sorafenib therapy was 82 days (range, 4-377 days). In 14 patients with Child-Pugh B, median duration of sorafenib therapy was 35 days (range, 10-287 days). In 16 patients (28.6%), sorafenib 400 mg b.i.d. was started. In 40 patients (71.4%), sorafenib 200 mg b.i.d. was started. In 16 of 16 patients (100%) with initiated sorafenib 400 mg b.i.d., dose reductions were required. In 29 of 40 patients (72.5%) with initiated sorafenib 200 mg b.i.d., dose reductions were required. Complete response was obtained in 1 patient (1.8%). PR was obtained in 5 patients (8.9%). SD was observed in 22 patients (39.3%). PD was observed in 26 patients (46.4%). In 2 patients (3.6%), treatment efficacy was not determined, since evaluation using dynamic CT was not performed. The objective response and disease control rates in the sorafenib group were 11.1 and 51.9%, respectively.

Adverse events associated with sorafenib treatment. During the follow-up period, 38 clinical adverse events with grade 3 or higher were observed in the sorafenib group as determined with National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (20). The details were as follows: rash in 2 patients (3.6%), hand-foot syndrome in 4 patients (7.1%), diarrhea in 8 patients (14.3%), appetite loss in 4 patients (7.1%), hepatotoxicity in 10 patients (17.9%), general fatigue in 5 patients (8.9%), high-grade fever in 3 patients (5.4%), and lung toxicity in 2 patients (3.6%).

Causes of discontinuation of sorafenib. In the sorafenib group, 45 patients (80.4%) discontinued sorafenib treatment. Causes of discontinuation were as follows: tumor progression in 21 patients, serious adverse events in 23 patients and patient's wish in 1 patient.

Causes of death. During the follow-up period, 48 patients (87.3%) died in the TACE group. Mortality in the TACE group was due to tumor progression in 34 patients (61.8%), liver failure in 13 patients (23.6%) and pneumonia in 1 patient (1.8%). During the follow-up period, 48 patients (85.7%) died in the sorafenib group. Mortality in the sorafenib group was due to tumor progression in 35 patients (62.5%), liver failure in 8 patients (14.3%) and pneumonia in 5 patients (8.9%).

Discussion

To our best knowledge, there have been no reliable data to date with regard to comparison between conventional TACE and sorafenib treatment for advanced HCC with vascular invasion and/or extrahepatic metastasis. Therefore, in the present study, we aimed to compare overall survival between stage IV HCC patients treated with conventional TACE and those treated with sorafenib.

Sorafenib was the first systemic chemotherapeutic agent to demonstrate a significant improvement in overall survival in patients with advanced HCC (6,7). However, Niu *et al* reported in their prospective comparative study that TACE was an effective treatment method for advanced HCC with PVTT compared to conservative treatment (21). Luo *et al* also reported in their prospective study that TACE was safe and feasible in selected HCC patients with PVTT and that it had survival benefit over conservative treatment (22). Chung *et al* also reported in their large retrospective study that TACE for advanced HCC patients with main portal vein invasion can be performed safely and may improve overall survival (23). Thus, several studies with favorable outcome in patients with stage IV HCC who received TACE have been reported. In the present study, in terms of overall survival, there were no significant differences between the TACE and the sorafenib groups. Our study results suggest that TACE could be a first-line treatment for stage IV HCC.

In terms of the objective response rate, there was no significant difference between the two groups (TACE group, 18.2%; sorafenib group, 11.1%; P=0.418). This result also suggests that TACE can be considered as a therapeutic option for the treatment of stage IV HCC.

In terms of the disease control rate, there was a significant difference between the two groups (TACE group, 74.5%; sorafenib group, 51.9%; P=0.017). Although the reason for this is unclear, TACE may be more effective at suppressing disease progression in stage IV HCC than sorafenib therapy.

Serum vascular endothelial growth factor (VEGF) levels increase with advancing HCC stages (24). Treatment of HCC with TACE is known to induce VEGF expression (25,26). In particular, in patients with incomplete response to TACE, TACE can induce the up-regulation of VEGF (24). Serum VEGF level was an independent predictor of survival in patients with advanced HCC (27,28). In the present study, there were 45 patients (81.8%) who did not obtain CR or PR in the TACE group. In these patients, in order to suppress VEGF and malignant angiogenesis, concurrent or sequential therapy with molecular targeted drugs such as sorafenib may be effective to optimize outcome (29).

Currently, in Japan, advanced HCCs are treated by hepatologists or radiologists. The former may be less familiar with the side effects of anticancer drugs, and the latter may not be prepared to manage problems related to underlying liver cirrhosis. Collaboration between hepatologists and radiologists is therefore essential to optimize outcome in the treatment of advanced HCC patients.

There are several limitations in the present study. First, this was a retrospective study. Second, in the sorafenib group, in 40 patients (71.4%), sorafenib 200 mg b.i.d. was started, leading to underestimated outcomes of patients treated with sorafenib, although in the SHARP and Asian Pacific trials, sorafenib 400 mg b.i.d. was started in all eligible patients. (6,7). Third, in the TACE group, previous therapies for HCC were not performed, whereas in the sorafenib group, previous locoregional therapies were performed, leading to bias. Therefore, a large prospective study will be required in the future. However, our study results demonstrated that in terms of overall survival, including subgroup analyses, there were no significant differences between the TACE group and the sorafenib group. In conclusion, TACE for stage IV HCC can be a first-line treatment as well as sorafenib therapy.

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＜症例報告＞

エンテカビル・ペグインターフェロンα-2b併用48週治療にてHBs抗原が消失したB型慢性肝炎の1例

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邉見慎一郎[1)]　石川　哲朗[1)]　齋藤　澄夫[1)]　西川　浩樹[1)]　喜多　竜一[1)]
岡部　純弘[1)]　木村　達[1)]　若狭　朋子[2)]　萩原　智[3)]　工藤　正俊[3)]

要旨：症例は65歳の日本人男性．2008年12月にB型慢性肝炎（Genotype C）指摘され，2009年12月よりエンテカビル（0.5 mg/日）とペグインターフェロンα-2b（80 μg/週）の48週間併用治療を開始．その後ウイルス量・HBe抗原価・HBs抗原価の減少を認めた．開始後44週時点でウイルス量は検出感度以下になるとともに，HBeセロコンバージョン・HBs抗原の消失，48週治療後半年以上経過した現在はHBsセロコンバージョンを維持している．HBs抗原自然消失例の報告は散見されるが，本症例は治療により引き起こされたHBs抗原消失例であり，そのような報告は少ない．また，本症例は治療前後の肝組織のcovalently closed circular DNA量や血清HBコア関連抗原量やHBc抗原の免疫染色を治療前後で比較できた点で，貴重な1例と考えられたため報告した．

索引用語：　B型慢性肝炎　　HBs抗原消失　　エンテカビル
ペグインターフェロンα-2b　　併用治療

はじめに

B型慢性肝炎に対してはこれまでインターフェロン治療，核酸アナログ治療が行われてきたが，治療によりHBs抗原が消失する例は少ない．今回我々はエンテカビル・ペグインターフェロンα-2b併用48週治療中にHBs抗原が消失したGenotype CのB型慢性肝炎の1例を経験したので，若干の文献的考察を加えて報告する．

症　例

症例：65歳男性．
主訴：B型慢性肝炎治療．
既往歴：なし．
生活歴：機会飲酒　喫煙なし．
家族歴：母　胃癌で他界（HBV感染は不明）．

現病歴：定期的に健診を受けていたが肝機能障害を指摘された覚えは無かった．2008年12月に心窩部不快感のため近医受診し，血液検査で軽度の肝障害認め，HBs抗原陽性であった．B型慢性肝炎の治療を希望し，2009年7月に当院初診受診した．

入院時現症：意識清明．身長165 cm，体重57Kg．体温36.1℃．脈拍60回/分．血圧100/60 mmHg．眼球結膜に黄染なし．眼瞼結膜に貧血なし．腹部は平坦・軟．肝脾触知せず．

血液生化学検査（**Table 1**）：AST 37 IU/L，ALT 55 IU/L，ALP 336 IU/L，γGTP 60 IU/L，T-Bil 0.7 mg/dlと軽度の肝障害を認めたが，肝予備能は保たれていた．また半年以上HBs抗原陽性は持続しており，B型慢性肝炎と診断された．HBVのGenotypeはCであり，ウイルスマーカーはHBs抗体陰性，HBc抗体陽性，HBe抗原陽性，HBe抗体陰性，ウイルス量はHBV DNA 7.9 Log copies/mlと高値であった．

なお，HBs抗原，HBs抗体，HBc抗体，HBe抗原，HBe抗体測定法はいずれもCLEIA法（富士レビオ）を

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＜受付日2011年9月13日＞＜採択日2011年12月8日＞

Table 1 Laboratory data on 2009/10/19 (admission)

Peripheral blood		Blood chemistry		Virus marker	
WBC	5480 /μl	TP	6.9 g/dl	HBs-Ag	(+) 345.9 COI
RBC	472×10⁴ /μl	Alb	4.3 g/dl	HBs-Ab	(−) 0.4 mIU/ml
Hb	14.7 g/dl	AST	37 IU/l	HBc-Ab	(+) 100 %
Ht	43.5 %	ALT	55 IU/l	HBe-Ag	(+) 1600 COI
Plt	18.8×10⁴ /μl	LDH	246 IU/l	HBe-Ab	(−) 0.1 %
		ALP	336 IU/l	HCV-Ab	(−)
Coagulation		γ-GTP	60 IU/l	HBV-DNA (Taqman assay)	7.9 Log copies/ml
PT	108 %	T.Bil	0.7 mg/dl	HBcrAg	>6.8 Log U/ml
APTT	29.0 sec	Ch-E	311 IU/l		
		AMY	105 IU/l	Tumor marker	
		BUN	13.5 mg/dl	AFP	2.8 ng/ml
		Cre	0.92 mg/dl	PIVKA-II	12 mAU/ml
		Na	141 mEq/l		
		K	4.5 mEq/l		
		Cl	103 mEq/l		
		CRP	<0.2 mg/dl		

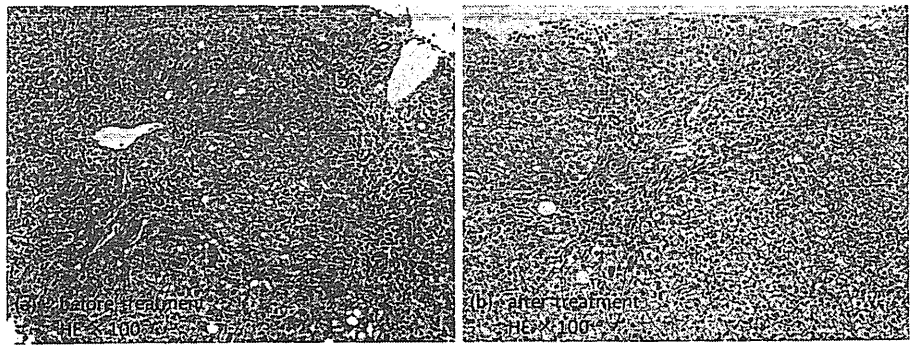

Fig. 1 Histopathological findings before and after treatment: (a) HE, ×100; (b) HE, ×100.
Liver tissue showed chronic active hepatitis with mild activity and moderate fibrosis (porto-portal bridging) in both (a) and (b). According to the "New *Inuyama* classification of chronic hepatitis, 1996", (a) and (b) are A1/F2.

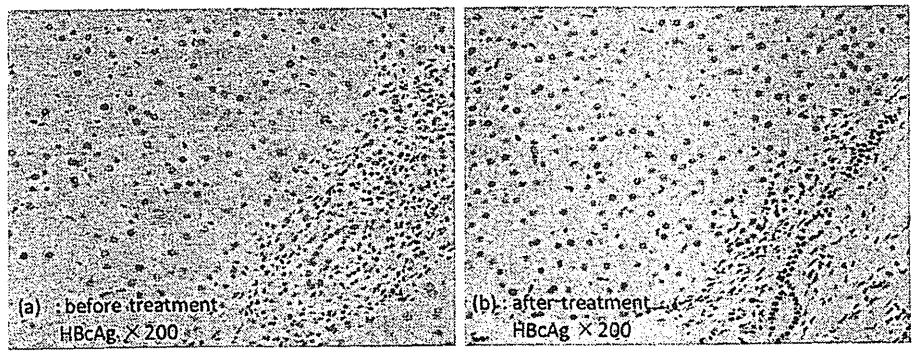

Fig. 3 Histopathological findings before and after treatment: (a) before treatment, HBcAg ×200; (b) after treatment, HBcAg ×200
Immunohistochemically, hepatocyte expression of HBcAg was positive before treatment (a), and negative after treatment (b). This suggested that treatment caused a diminution in expression of HBcAg in the hepatocytes.

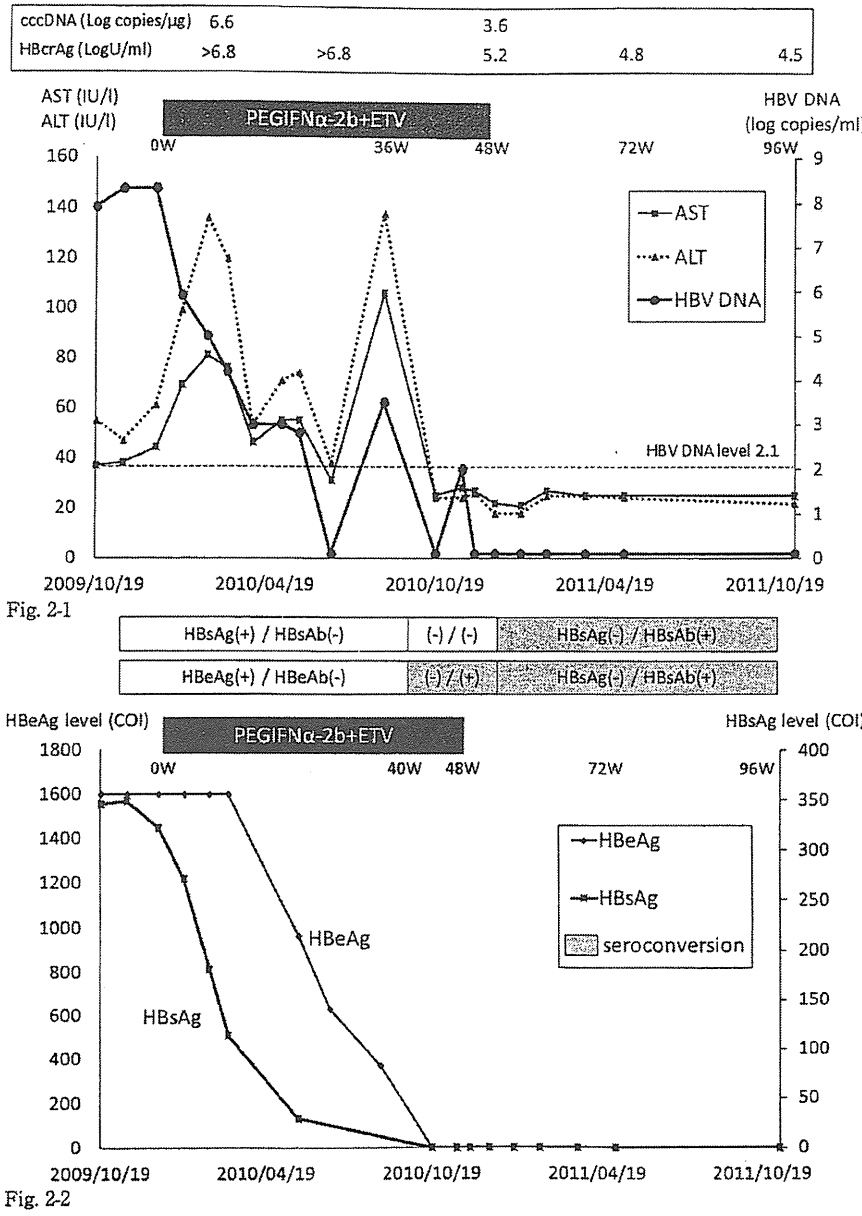

Fig. 2 Clinical course

用いた.

画像検査：腹部単純CTにて異常所見認めず，腹部超音波検査にて異常所見認めず.

入院後経過：入院後肝生検施行したところ，Piecemeal necrosisは軽度であり，門脈架橋線維化も軽度見られ，A1/F2（新犬山分類[1]より）の診断であった（Fig. 1）. 肝組織のcovalently closed circular DNA（cccDNA）量は6.6 Log copies/μgであった.

2009年12月21日より，Drug-freeを目的とした前向き臨床試験[B型慢性肝炎患者に対するペグインターフェ

ロン-alpha2bとentecavir併用療法の有効性に関する研究，承認番号153]に参加し，エンテカビル・ペグインターフェロンα-2b併用治療を開始．エンテカビルを0.5 mg/日内服し，ペグインターフェロンα-2bを80μg/週で48週間併用投与した．

副作用は治療期間中，微熱程度で問題となる合併症認めず，治療を安全に行えた．治療開始後徐々にウイルス量・HBe抗原価・HBs抗原価の低下を認め，肝酵素は一過性に軽度上昇したが，その後減少認めた．28週時点で<2.1 Log copies/mlと低下していた血清ウイルス量は36週時点で3.5 Log copies/mlと上昇し，肝酵素もAST 31 IU/L, ALT 38 IU/LがAST 106 IU/L, ALT 138 IU/Lとフレアアップしたが，開始後44週時点でウイルス量は検出感度以下になるとともに，HBe抗原・HBs抗原の消失・HBeセロコンバージョンを認め，肝酵素は正常化した．また，56週時点でHBsセロコンバージョンを認め，治療終了後48週経過した時点でも維持している（Fig. 2-1，Fig. 2-2）．なお，治療終了時点（48週後）の肝生検では肝炎活動性・線維化ともに大きな変化なく，A1/F2の診断であった（Fig. 1）．肝組織のcccDNA量は3.6 Log copies/μgであり，著明に低下していた（⊿−3.0 Log copies/μg）．また，HBコア関連抗原（HBcrAg）は治療開始前の>6.8 Log U/mlから，治療終了後は5.2 Log U/ml，治療終了より48週後で4.5 Log U/mlと低下していた（Fig. 2-1）．また，治療前後の肝生検組織のHBc抗原の免疫染色は，著明に染色性が低下していた（Fig. 3）．

考　察

諸家の報告によると，アジアでのB型慢性肝炎患者のHBs抗原の自然消失率は年間0.07〜0.43％程度[2)3)]である．B型慢性肝炎のHBs抗原消失後の発癌率は非常に低く，予後良好で肝疾患関連死はほとんどないと報告されている[4)〜6)]．今日的にはHBs抗原の陰性化はB型慢性肝炎治療の目標と考えられるが，本邦では治療反応性の低いGenotype Cが多く，現実的にはその達成は困難である．

近年，B型慢性肝炎にペグインターフェロンαが治療に有効であるという報告があり，HBe抗原陰性例では3％程度で[7)]，HBe抗原陽性例では3〜7％程度で[8)〜10)]，HBs抗原消失例が報告されている．ただし，ペグインターフェロンα-2a治療において，アジア人は西洋人に比較しHBs抗原消失率が低いと報告されている[2)8)]．

本例は，B型慢性肝炎の治療として，より高い抗ウイルス作用を期待してペグインターフェロンα-2bとエンテカビルの48週間併用治療を試みた．なお，B型慢性肝炎に対するペグインターフェロンα-2b投与は保険未承認であり，当院倫理委員会の承認を得て施行した．国外ではペグインターフェロンα-2aやペグインターフェロンα-2bの，ラミブジンとの併用治療に関してはRCTによる多数例の報告があり，HBe抗原陽性・陰性いずれの症例にも同時併用治療によるペグインターフェロン単剤治療への上乗せ効果は否定されている[7)〜9)]．一方，ドイツからペグインターフェロンα-2bとアデホビルの48週併用治療の報告があり，少数例の検討ではあるが，血清学的にも組織学的にも強い抗ウイルス効果が報告された[11)]．ラミブジンやアデホビルよりも抗ウイルス効果が強く，薬剤耐性率も低いエンテカビル[12)〜14)]については，ペグインターフェロンとの併用治療で未だ報告なく，本症例は貴重な症例であると考える．

本症例は血清HBV DNA量・肝組織cccDNA量・血清HBcrAg量のいずれも高ウイルス量であったが，併用治療後には血清HBV DNA量は消失し，肝組織cccDNA量や血清HBcrAg量は著減するとともにHBc抗原免疫染色の染色性は消失した．血清HBs抗原量や肝組織cccDNA量や血清HBcrAg量や肝組織HBc抗原染色性には治療相関があると考えられており[11)15)16)]，本症例は治療中にいずれのマーカーも低下し，ウイルス学的著効を得た．

核酸アナログ単剤治療においても，長期間投与で肝内cccDNA量が低下することが知られている[17)]．核酸アナログ治療にはcccDNA合成への直接的な影響はないが，血中ウイルスの著減により再利用できるヌクレオカプシドを減らしcccDNA合成阻害する[11)17)]，もしくは炎症性サイトカインによる長期的なウイルス合成阻害[11)]などがcccDNA低下の主な作用機序であると考えられている一方，インターフェロン治療は，ウイルス合成を抑制するようなサイトカインの産生や，細胞傷害性T細胞を活動させ感染肝細胞破壊を促進させることなどが主な作用機序であると考えられており[11)]，併用治療にはそれらの作用が組み合わさることが期待される．

最近の報告では，インターフェロン治療による早期の段階でのHBs抗原価の低下が治療効果と相関するとされており[2)18)]，本症例の特徴として，治療前よりHBs抗原量が低く，早期の治療反応性も良好であったことが，HBs抗原の消失という良好な結果に繋がった可能性がある．

また，HBe抗原陽性のB型慢性肝炎における治療中・治療後のAST/ALTのフレアアップは治療反応性を示す重要な因子であることが知られているが[19]，本例も治療中の一時的なフレアアップの後にHBe抗原・HBs抗原の消失を認めた．

本症例において，ペグインターフェロンα-2bのエンテカビルとの併用治療は有効であったが，あくまでも一症例報告であり，今後症例数を重ねて検討する必要がある．

結　語

エンテカビル＋ペグインターフェロンα-2b併用48週治療にてHBs抗原が消失したB型慢性肝炎の1例を経験したため報告した．ペグインターフェロンは今後B型慢性肝炎にも，使用回数が増える可能性の高い薬剤であり，本症例のようにエンテカビルとの併用治療は新しいB型慢性肝炎の治療法となる可能性もある．

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A case of chronic hepatitis B which achieved hepatitis B surface antigen seroclearance during combination therapy with peginterferon alfa-2b and entecavir

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A 65-year-old Japanese male with chronic hepatitis B (CH-B) diagnosed in December 2008 was referred to our department in July 2009. He started combination therapy with peginterferon alfa-2b (80 μg/week) and entecavir (0.5 mg/day) for 48 weeks from December 2009. At the initiation of therapy, his significant laboratory test results were as follows: alanine aminotransferase (ALT) 55 IU/l, aspartate aminotransferase (AST) 37 IU/l, hepatitis B surface antigen (HBsAg) positive, hepatitis B e antigen (HBeAg) positive, hepatitis B virus (HBV) DNA levels 7.9 Log copies/ml. HBV DNA, HBsAg and HBeAg levels decreased progressively with therapy. After 36 weeks, HBV DNA, AST and ALT levels flared up, but after 44 weeks, HBV DNA levels decreased below 2.1 Log copies/ml and HBeAg seroconversion and HBsAg seroclearance were achieved. After 72 weeks he maintained HBsAg seroclearance and achieved a sustained viral response. Cases of spontaneous HBsAg seroclearance have been reported previously, but HBsAg seroclearance caused by combination therapy with peginterferon alfa-2b and entecavir has not been reported. Pre- and post-treatment cccDNA load in liver tissue, hepatitis B virus core-related antigen (HBcrAg) concentration in serum and expression of hepatitis B core antigen (HBcAg) in hepatocyte were compared, and it was found that all were drastically decreased. The present study suggests that these reduction appeared to contribute to the successful outcome of this therapy.

Key words: chronic hepatitis B HBsAg seroclearance entecavir peginterferon alfa-2b combination therapy

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肝細胞癌の分子標的薬治療効果判定における modified RECIST の妥当性と問題点～当院での経験より

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