Table 1. Patient characteristics of 1056 sustained responders to interferon therapy given for chronic hepatitis C

		Number of patients
Host-related variables		
Age (years)	Median (range)	50 (11–76)
Sex	Male	711 (67%)
History of blood transfusion	Positive	266 (27%)
Alcohol abuse[a]	Positive	78 (8%)
Smoking habit[b]	Positive	248 (38%)
HCV viral load	High ($\geq 10^6$)	159 (21%)
HCV serologic group	Group 1	372
	Group 2	466
Hepatitis B surface antigen	Positive	17 (2%)
Treatment-related variables		
Interferon type	α	829 (79%)
	β	166 (16%)
	α + β	61 (6%)
Total amount of interferon (MU)	Median (range)	480 (42–1740)
Treatment period (weeks)	Median (range)	22 (2–56)
Prior interferon therapy	Positive	87

HCV, hepatitis C virus
[a] Alcohol intake, ≥80 g/day × 5 years
[b] Smoking habit, ≥20 cigarettes/day for ≥10 years

years; incidence curves of HCC were calculated by the Kaplan-Meier method; and differences in survival were evaluated by log rank tests. Hazard ratios and trend *P* values were calculated by treating the categories as ordinal variables. The Cox proportional hazard model was used to determine the most significant variables related to the development of HCC. All patients were then assigned a risk index value for the development of HCC, as follows: the value of each factor in the final model was multiplied by its corresponding regression coefficient, and these values were totaled to obtain the risk index for each patient. Stratification of the patients was conducted on the basis of this risk index. All *P* values were two-tailed and were considered significant when less than 0.05.

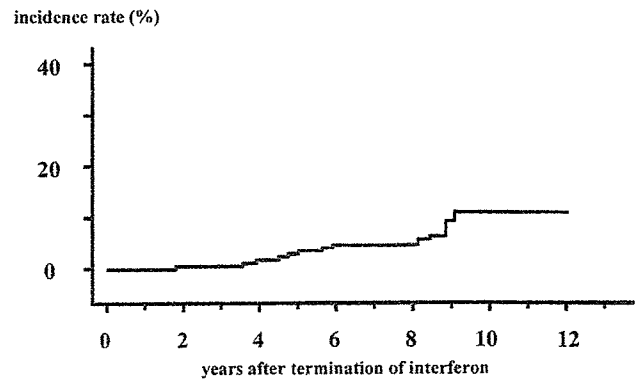

Fig. 1. Cumulative incidence of hepatocellular carcinoma in 1056 sustained responders to interferon therapy given for chronic hepatitis C

Results

Patient characteristics

Table 1 summarizes the patient characteristics of the 1056 sustained responders to IFN therapy given for chronic hepatitis C. The median age was 50 years (range, 11–76) years, and there were 711 men and 345 women (sex ratio, 2.1:1). Hepatitis B surface antigen was positive in 17 patients (2%). The HCV serological group was group 1 in 372 patients and group 2 in 466 patients, and thus a higher proportion of patients were in serological group 2. A total of 829 patients (79%) received IFN-α, 166 patients (16%) received IFN-β, and 61 patients (6%) received both. The median dose and duration of IFN administration were 480 MU and 22 weeks, respectively. No patients received peginterferon or combination therapy with ribavirin, and 87 patients (8%) received more than two cycles of IFN therapy.

Incidence of HCC

Twenty-nine of the 1056 sustained responders developed HCC, with a median follow-up period of 4.7 years. The incidence of HCC per 100 person-years was 0.56 (95% confidence interval, 0.35–0.76), and the incidences of HCC at 3, 5, 7, and 10 years after the termination of IFN therapy were 0.5%, 3.3%, 4.9%, and 11.1%, respectively (Fig. 1).

Univariate analyses

On univariate analysis (Table 2), age more than 60 years, positive smoking habit, platelet count less than $15 \times 10^4/mm^3$, aspartate aminotransferase (AST) more than 100 IU/l, prothrombin time less than 80%, and higher fibrosis stage (incidence of HCC per 100 person-years: F0, 0.00; F1, 0.27; F2, 0.47; F3, 0.62; F4, 1.31) were significant risk factors associated with the development of HCC. Alcohol abuse, total bilirubin, albumin, alanine aminotransferase, virological variables (viral load, serological group), tumor markers (alpha-fetoprotein, protein induced by vitamin K absence or antagonist-II), and treatment-related variables (treatment period, IFN type, total amount of IFN) were not significant risk factors.

Multivariate analyses

All variables whose P values were less than 0.20 on the univariate analyses were entered into the multivariate analyses (Table 3). However, history of blood transfusion, smoking habit, prothrombin time, and indocyanine green retention rate at 15 min (ICG R15) were not included in the model because inadequate data were available. Multivariate regression analysis, which assessed the independent predictive importance of each variable studied for the development of HCC, showed that older age, higher serum AST level, and lower platelet count were significantly related to the development of HCC.

Risk groups based on the regression model

For the clinical application of these findings, a risk index was calculated based on the regression coefficients derived from the three variables identified by multivariate analysis. The index equation was as follows: $1.14 \times$ (0, age $\leq$ 60 years; 1, age $>$ 60 years) + $1.13 \times$ (0, AST $\leq$ 100 IU/l; 1, AST $>$ 100 IU/l) + $1.02 \times$ (0, platelet count $\geq 15 \times 10^4/mm^3$; 1, platelet count $< 15 \times 10^4/mm^3$). The risk index was $\ln[hi(t)/h_0(t)]$, where $hi(t)/h_0(t)$ was the relative risk of the development of HCC for the i-th patient. The index values ranged from 0.00 to 3.29. The patients were then classified into three groups according to the risk index, as follows: low risk, risk index less than 1.00 (equivalent to patients with none of the three risk factors); intermediate risk, risk index from 1.00 to 2.00 (equivalent to patients with one of the three risk factors); and high risk, risk index greater than 2.00 (equivalent to patients with two or more of the three risk factors). The incidence curves for the three groups are shown in Fig. 2. The incidence rates of HCC per 100 person-years (95% confidence interval) in the low-, intermediate-, and high-risk groups were 0.11 (0.00–0.26), 0.44 (0.11–0.77), and 1.98 (1.09–2.87), respectively. There was a significant difference in survival time among the three groups ($P < 0.0001$).

Clinical features of HCC

The characteristics of the 29 patients in whom HCC developed after sustained response are shown in Table 4. All patients were HCV RNA-negative (determined by using qualitative HCV RNA assay), at the time of diagnosis of HCC. Twenty-five patients (86%) were aged 60 years or more, and 24 patients (83%) were men. Among the 13 patients in whom liver biopsy was done at the time of diagnosis of HCC, A0, A1, and A2 histological activity was observed in 5 (38%), 6 (46%), and 2 (15%) patients, respectively. F0, F1, F2, F3, and F4 histological stages were observed in 1 (8%), 1 (8%), 7 (54%), 2 (15%), and 2 (15%) patients, respectively. The median period from the termination of IFN therapy to the development of HCC was 4.6 years (range, 1.4–9.0 years), and there were 11 patients (38%) in whom HCC was detected more than 5 years after the termination of IFN therapy. The periods and methods of medical follow-up examination after the end of IFN therapy varied among the patients, and 8 patients did not receive a sufficient post-treatment medical examination. Among them, HCC of 5 cm or more in size was detected in 5 patients (63%).

Discussion

IFN is already widely used as a standard therapeutic modality for chronic hepatitis C.[5–9] It is generally assumed that eradication of HCV by IFN halts the progression of the disease and prevents clinical complications, including the development of HCC.[5,7,10–14] However, there have been reports of several patients in whom HCC developed after successful IFN therapy.[5,10–25] The incidence and clinical features of HCC, the risk factors for the disease, and the mechanism of carcinogenesis in these patients have not been fully elucidated, because the development of HCC is very rare in sustained responders to IFN therapy. This prompted us to perform a multicenter retrospective cohort study to gather clinical data on such patients.

Of all 1056 sustained responders to IFN therapy in the 16 hospitals in the study, 29 developed HCC, with a median period to development of 4.7 years, and the incidence of HCC was 0.56 (95% confidence interval, 0.35–0.76) per 100 person-years. This value was consistent with the results of previous studies of small numbers of sustained responders to IFN who developed HCC.[5,11–14,20,21–25] This rate was considerably lower than that in IFN-refractory patients or HCV-positive pa-

Table 2. Univariate analysis of 1056 sustained responders in relation to development of HCC

Variables		No. of patients	No. of patients developing HCC	Incidence (95% CI) (/100 person-years)	Hazard ratio (95% CI)	*P* value (log rank)
Host-related variables						
Age	≤60 years	840	13	0.32 (0.14–0.49)	—	
	>60 years	216	16	1.43 (0.73–2.13)	4.23 (2.04–8.80)	0.001
Sex	Male	711	24	0.67 (0.40–0.94)	—	
	Female	345	5	0.30 (0.04–0.57)	0.47 (0.18–1.23)	0.12
History of blood transfusion	Positive	266	11	0.80 (0.33–1.28)	—	
	Negative	723	16	0.45 (0.23–0.67)	0.60 (0.28–1.30)	0.19
Alcohol abuse[a]	Positive	78	2	0.53 (0.00–1.26)	—	
	Negative	946	26	0.56 (0.34–0.77)	1.05 (0.25–4.42)	0.95
Smoking habit[b]	Positive	248	14	1.16 (0.55–1.77)	—	
	Negative	405	7	0.36 (0.09–0.62)	0.30 (0.12–0.75)	0.009
HCV viral load	High (≥10^6)	159	1	0.15 (0.00–0.45)	—	
	Low (<10^6)	593	11	0.42 (0.17–0.66)	2.68 (0.35–20.77)	0.35
HCV serological group	Group 1	372	5	0.27 (0.03–0.52)	—	
	Group 2	466	10	0.47 (0.18–0.76)	1.78 (0.60–5.26)	0.30
Hepatitis B surface antigen	Positive	17	0	0.00		
	Negative	1008	27	0.54 (0.34–0.75)	[c]	0.56
Platelet count (×10^4/mm^3)	≥15	568	7	0.27 (0.07–0.46)	—	
	<15	358	21	1.15 (0.66–1.65)	3.95 (1.68–9.30)	0.002
Total bilirubin (mg/dl)	≥1.0	207	8	0.75 (0.23–1.27)	—	
	<1.0	824	21	0.52 (0.30–0.75)	0.37 (0.32–1.65)	0.45
Albumin (g/dl)	>4.0	564	17	0.59 (0.31–0.87)	—	
	<4.0	396	8	0.42 (0.13–0.72)	0.78 (0.34–1.80)	0.56
Aspartate aminotransferase (IU/l)	>100	196	13	1.26 (0.57–1.94)	—	
	≤100	844	16	0.39 (0.20–0.58)	0.35 (0.17–0.73)	0.005
Alanine aminotransferase (IU/l)	>100	459	17	0.73 (0.38–1.07)	—	
	≤100	591	12	0.42 (0.18–0.66)	0.63 (0.30–1.32)	0.22
Prothrombin time (%)	≥80	493	9	0.39 (0.14–0.65)	—	
	<80	158	10	1.19 (0.45–1.93)	2.72 (1.10–6.74)	0.03
ICG R15 (%)	≥10	322	9	0.52 (0.18–0.86)	—	
	<10	274	1	0.08 (0.00–0.23)	0.18 (0.02–1.44)	0.11
Alpha-fetoprotein (ng/ml)	>20	66	2	0.58 (0.00–1.39)	—	
	<20	554	16	0.58 (0.30–0.87)	1.10 (0.25–4.81)	0.78
PIVKA-II (AU/ml)	>0.063	42	0	0.00		
	≤0.063	235	8	0.66 (0.20–1.12)	[c]	0.63
Histological activity grade	A0 (No)	12	0	0.00		
	A1 (Mild)	309	6	0.40 (0.08–0.73)		
	A2 (Moderate)	359	11	0.64 (0.26–1.01)		
	A3 (Severe)	169	5	0.61 (0.07–1.14)	1.28 (0.74–2.21)	0.39
Histological fibrosis stage	F0 (No)	26	0	0.00		
	F1 (Mild)	405	5	0.27 (0.03–0.50)		
	F2 (Moderate)	301	7	0.47 (0.12–0.82)		
	F3 (Severe)	170	6	0.62 (0.12–1.11)		
	F4 (Cirrhosis)	97	4	1.31 (0.03–2.60)	1.56 (1.03–2.36)	0.03
Treatment-related variables						
Treatment period (weeks)	>24	472	17	0.73 (0.38–1.08)		
	<24	584	12	0.41 (0.18–0.65)	0.56 (0.27–1.16)	0.11
Interferon type	α	829	25	0.61 (0.37–0.85)	—	
	β	166	4	0.55 (0.01–1.10)	0.99 (0.34–2.86)	0.98
	α + β	61	0	0.00	[c]	
Total amount of interferon (MU)	>500	491	10	0.42 (0.16–0.68)	—	
	≤500	534	16	0.60 (0.31–0.89)	1.34 (0.61–2.95)	0.47
Prior interferon therapy	Positive	87	2	0.46 (0.00–1.10)	—	
	Negative	955	27	0.57 (0.36–0.79)	1.17 (0.28–5.00)	0.82

HCC, hepatocellular carcinoma; CI, confidence interval; HCV, hepatitis C virus; ICG R15, indocyanine green retention rate at 15 min; PIVKA II, protein induced by vitamin K absence or antagonist-II; —; reference category

[a] Alcohol intake ≥80 g/day + 5 years

[b] Smoking habit, >20 cigarettes/day for >10 years

[c] not estimated

tients who did not receive IFN therapy, which has been reported to be 1.4%–7% yearly,[4–7,10–13,21–24] and it was obvious that IFN therapy decreased the risk of HCC in sustained responders. However, the incidence of HCC gradually increased over a period of at least 9 years after the termination of IFN therapy (Fig. 1). This suggests that the risk of HCC is not completely eliminated in patients who have a sustained response to IFN therapy,

at least for up to 9 years following cessation of the treatment.

Identification of the risk factors for the development of HCC in sustained responders is important, so that high-risk patients can be screened carefully for early detection of HCC and given potentially curative treatments such as hepatic resection; such patients generally have a good hepatic reserve after the elimination of HCV. Among the variables we investigated, multivariate analysis showed age to be an independent risk factor. As the patient ages, the period of HCV infection becomes longer, and the liver becomes more severely cirrhotic. Therefore, advanced age may simply represent the progression of associated liver disease. These findings are compatible with previous reports of the development of HCC in patients with chronic hepatitis C.[11–14,20–22]

Serum AST level and platelet counts were also independent risk factors in the present study. Some studies have reported that increased AST level and decreased platelet count are correlated with the progression of liver fibrosis,[33–34] which has been reported to be one of the most important risk factors for the development of HCC in patients with chronic hepatitis C.[5,11–13,21] Progression of liver fibrosis may reduce the clearance of AST,[35] leading to increased serum AST levels.[36] This progression is also associated with decreased production of thrombopoietin by hepatocytes[37] and progressive hypersplenism with worsening portal hypertension;[38] and, hence, reduced platelet production and increased platelet destruction. Moreover, in the present study, these factors were strongly associated with histological stage (Pearson's correlation coefficient; $P < 0.0001$). Therefore, increased AST level and decreased platelet count may reflect more progressive liver fibrosis.

For the clinical application of these findings, we proposed a risk index based on the independent risk factors. Patients were classified into three groups, with low, intermediate, and high risk ($P < 0.0001$ for difference in survival time among the three groups; Fig. 2). This index can be easily calculated, because it is based on variables obtained during routine laboratory examinations before IFN therapy is begun. This index, therefore, may be helpful in assessing the risk of development of HCC after sustained response to IFN therapy, although it is also important to validate this risk index by applying it to other populations of patients. Patients in the high-risk group (incidence rate, 1.98 per 100 person-years) may benefit from regular diagnostic imaging for the early detection of HCC.

In the analysis of the clinical features of HCC there were no specific findings. The period to the development of HCC after IFN therapy (median, 4.6 years; 1.4–9.0 range, years) was variable. HCC developed even in two patients whose liver showed improvement to mild fibrosis (stage F0 or F1) and in five patients whose liver improved to no activity (A0) after IFN therapy. The follow-up periods and methods for the detection of HCC after the termination of IFN therapy varied among the patients, and in some patients HCC was detected at far more advanced stages than in others, because of insufficient follow up after IFN therapy. This finding may suggest the need for regular follow up by diagnostic imaging, even after sustained response to IFN therapy for chronic hepatitis C, especially in the high-risk group.

Our study involved some uncertainties. First, because the study was retrospective, many data items were missing from the replies to the data collection instrument, and we had to ignore unmeasured or unrecorded data when conducting the statistical analyses. In the multivariate analysis, therefore, only variables whose P values were less than 0.20 on the univariate analysis were entered. Also, history of blood transfusion, smoking habit, prothrombin time, and ICG R15, whose P values were lower than 0.20, had to be excluded from the model because of missing data; these factors were potentially significant on multivariate analysis. Secondly, we sought information on serum hepatitis B virus DNA

Table 3. Significant risk factors identified in 1056 sustained responders, as determined by multivariate analysis with the Cox proportional hazard model

Variable	Hazard ratio (95% confidence interval)	P value
Age	3.13 (1.32–7.42)	0.01
Aspartate aminotransferase	3.10 (1.31–7.31)	0.01
Platelet count	2.78 (1.07–7.20)	0.04

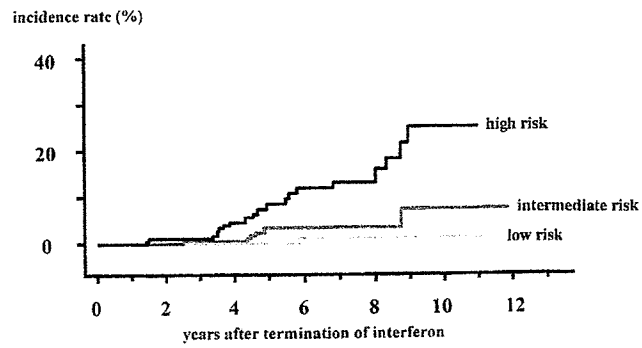

Fig. 2. Cumulative incidence of hepatocellular carcinoma for the three groups determined by a risk index based on the results of multivariate analysis. Low risk (risk index < 1.00); intermediate risk (risk index from 1.10 to 2.00); high risk (risk index, ≥2.00)

Table 4. Clinical features at the time of diagnosis of HCC in 29 patients who developed hepatocellular carcinoma after sustained response to interferon therapy given for chronic hepatitis C

Age (years)	Sex	HCV RNA	HBs Ag	Histological fibrosis stage	Histological activity grade	AFP (ng/ml)	PIVKA II (AU/ml)	Number of tumors
64	Male	Negative	Negative	NA	NA	2	0	4
60	Male	Negative	Negative	NA	NA	51	0.211	1
38	Male	Negative	Negative	NA	NA	4.3	NA	>5
67	Male	Negative	Negative	F4	A0	4.2	0.033	1
75	Male	Negative	Negative	F1	A1	5	0.054	1
65	Female	Negative	Negative	NA	NA	5	0.029	1
62	Male	Negative	Negative	NA	NA	3	NA	1
61	Male	Negative	Negative	F2	A0	3	0.001	1
64	Male	Negative	Negative	F2	A0	4	0.426	1
70	Male	Negative	Negative	NA	NA	46 000	NA	1
64	Male	Negative	Negative	NA	NA	146	0.049	1
54	Female	Negative	Negative	F3	A1	2165	6690	1
65	Male	Negative	Negative	F4	A2	25.9	0.015	>5
61	Male	Negative	Negative	F2	A1	4	1.79	1
64	Male	Negative	Negative	F2	A0	NA	NA	1
63	Male	Negative	Negative	NA	NA	135.3	0.06	1
67	Male	Negative	Negative	NA	NA	3.5	0.013	1
75	Male	Negative	Negative	NA	NA	2	NA	1
62	Male	Negative	Negative	F2	A1	1026	13.32	1
62	Male	Negative	Negative	F2	A1	2.3	1.79	1
68	Female	Negative	Negative	F3	A2	9.1	0.016	1
59	Male	Negative	Negative	F0	A0	29	0.029	1
70	Male	Negative	Negative	NA	NA	488.3	601 371	1
54	Male	Negative	Negative	NA	NA	258	2.1	1
68	Female	Negative	Negative	NA	NA	2.8	0.023	1
60	Male	Negative	Negative	F2	A1	3.2	0.023	1
70	Male	Negative	Negative	NA	NA	5463	6.566	2
70	Female	Negative	Negative	NA	NA	464.2	NA	1
77	Male	Negative	Negative	NA	NA	72	0.136	2

NA, not available; HBs Ag, hepatitis B surface antigen; AFP, alpha-fetoprotein; PIVKA II, protein induced by vitamin K absence or antagonist-II; Vp, portal vein invasion; Vv, hepatic vein invasion; B, bile duct invasion; US, ultrasonography; CT, computed tomography

in sustained responders in whom HCC developed after successful IFN therapy, but data could be obtained for only two patients, who were negative for hepatitis B virus DNA. We cannot rule out the presence of occult hepatitis B virus in the other patients, although all patients were negative for hepatitis B antigen. In spite of these uncertainties, this study represents a comprehensive analysis of HCC developing after sustained response to IFN therapy, because we were able to collect clinical data for a large number of sustained responders at 16 major hospitals.

In this study, we encountered 29 patients in whom HCC developed after successful IFN therapy, but the reason why HCC developed in these sustained responders is unclear. The existence of a small undetected HCC at the time of IFN therapy may have been responsible for the appearance of HCC after the sustained response to IFN therapy. However, in 11 patients (38%), HCC was detected more than 5 years after IFN therapy, and the incidence of HCC gradually increased for at least 9 years after IFN therapy. Considering the late onset of HCC in these patients, we cannot neglect the possibility of the de-novo development of HCC after the eradication of HCV. HCV is a single-stranded RNA virus without a DNA intermediate in its replicative cycle, so that the integration of HCV nucleic acid sequences into the host genome seems unlikely. Therefore, it is difficult to believe that HCV itself is a causative factor of HCC in the absence of chronic inflammation, liver cell necrosis and regeneration, and extensive fibrosis. It is probable that carcinogenesis is not a single-step event, but a complex multistep process. Future studies should aim to define the basic oncogenic mechanisms by which sustained responders to IFN develop HCC. Exploration of these mechanisms may point the way toward new strategies for the prevention of HCC.

In conclusion, some patients showing a sustained response to IFN therapy given for chronic hepatitis C demonstrated potential for the development of HCC for up to 9 years following cessation of the treatment. This suggests that the risk of HCC in sustained responders is not completely eliminated. The establishment of risk factors and an index for the development of HCC may be useful in determining follow-up strategy in patients after a sustained response to IFN therapy given for chronic hepatitis.

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Prognostic factors in patients with advanced hepatocellular carcinoma receiving hepatic arterial infusion chemotherapy

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Background. The prognosis of patients with advanced hepatocellular carcinoma (HCC) is poor. We aimed to clarify the prognostic factors in patients with advanced HCC receiving hepatic arterial infusion chemotherapy (HAIC). ***Methods.*** Forty-four HCC patients were treated with HAIC, using low-dose cisplatin (CDDP) and 5-fluorouracil (5-FU) with/without leucovorin (or isovorin). Of these 44 patients, 15 received low-dose CDDP and 5-FU, and 29 received low-dose CDDP, 5-FU, and leucovorin or isovorin. Prognostic factors were evaluated by univariate and multivariate analyses of patient and disease characteristics. ***Results.*** Of all patients, 5 and 12 patients respectively, exhibited a complete response (CR) and a partial response (PR) (response rate, 38%). The response rate (48.3%) in the low-dose CDDP and 5-FU with leucovorin/isovorin group was significantly better than that (20%) in the low-dose CDDP and 5-FU group ($P = 0.002$). The 1-, 2-, 3-, and 5-year cumulative survival rates of the 44 patients were 39%, 18%, 12%, and 9%, respectively. The regimen using low-dose CDDP and 5-FU with leucovorin/isovorin tended to improve survival rates ($P = 0.097$). Univariate and multivariate analyses showed the same variables—the Child-Pugh score ($P = 0.013$, $P = 0.018$), α-fetoprotein (AFP) level ($P = 0.010$, $P = 0.009$), and therapeutic effect after HAIC ($P = 0.003$, P 0.01), respectively, to be significant prognostic factors. ***Conclusions.*** Patients who had advanced HCC with favorable hepatic reserve capacity and a lower AFP level were suitable candidates for HAIC. Moreover, the regimen using low-dose CDDP and 5-FU with leucovorin/isovorin may be suitable for advanced HCC patients, because of the improvement in the response rate and survival compared with the low-dose CDDP and 5-FU regimen without leucovorin/isovorin.

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Key words: advanced hepatocellular carcinoma, hepatic arterial infusion chemotherapy, biochemical modulator, prognostic factor

Introduction

The prognosis of advanced hepatocellular carcinoma (HCC) remains poor, especially for patients with portal vein tumor thrombosis (PVTT).[1–4] Almost all patients with advanced HCC die within several months of diagnosis. Therefore, patients with unresectable HCC are usually treated with hepatic arterial infusion chemotherapy (HAIC). HAIC, with several anticancer agents[4–6] and a combination of antiproliferative agents,[7,8] is useful for patients with advanced HCC. However, there are not yet any standard chemotherapeutic regimens for advanced HCC.

We previously designed a new regimen using cisplatin (CDDP), 5-fluorouracil (5-FU), and leucovorin. Leucovorin is a biochemical modulator of 5-FU.[9–11] We reported the usefulness of HAIC using low-dose CDDP and 5-FU with leucovorin in patients with advanced HCC. In addition, we found that the response rate and survival for the low-dose CDDP and 5-FU with leucovorin regimen were significantly better than those for the low-dose CDDP and 5-FU-alone regimen, in a randomized study.[12] Furthermore, we investigated the efficacy of our regimen with high-dose leucovorin, using isovorin, which is an active form of leucovorin. We reported that there were no significant differences in the response rate, the survival rate, and the toxicity between low-dose leucovorin and high-dose leucovorin.[13] In the current study, we investigated the factors that influenced survival by applying univariate and multivariate analyses to 44 patients with advanced HCC treated with HAIC using low-dose CDDP and 5-FU with/without leucovorin (or isovorin).

Table 1. Clinical characteristics of 44 patients with hepatocellular carcinoma

Clinical characteristics	
Sex (male/female)	38/6
Age (younger than 65 years/66 years and older)	28/16
HCV (+/−)	32/12
Child-Pugh (A/B)[a]	29/15
Previous treatment (yes/no)	35/9
Plasma concentration of AFP (<1000 ng/ml/≧1000 ng/ml)	24/20
Plasma concentration of DCP (<1000 mAU/ml/≧1000 mAU/ml)	27/17
Maximum tumor size (<50 mm/≧50 mm)	22/22
Tumor stage (II/III/IV A/IV B)[b]	6/16/19/3
Grade of portal invasion (Vp 0/1/2/3/4)[c]	23/3/4/7/7
Leucovorin or isovorin (yes/no)	29/15
Additional therapy (yes/no)	20/24

HCV, hepatitis C virus; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin; Vp, portal tumor thrombosis
[a] Child-Pugh stage
[b] According to the Liver Cancer Study Group of Japan
[c] Portal invasion. Vp1, tumor thrombus in a third or more of the peripheral branches; Vp2, in the second branch; Vp3, in the first branch; Vp4, in the trunk

Patients and methods

Patients

Forty-four patients with unresectable HCC who were admitted to the Department of Gastroenterology and Hepatology, Yamaguchi University School of Medicine, were enrolled in the current study between July 1997 and March 2002. Disease was considered unresectable when there was locally advanced disease too extensive for resection, bilobar disease, extrahepatic metastasis, or PVTT. Of these 44 patients, 15 patients underwent HAIC using low-dose cisplatin (CDDP) and 5-FU, and 29 underwent HAIC using low-dose CDDP and 5-FU with leucovorin or isovorin. The diagnosis of HCC was made by imaging studies and was based on elevated serum levels of α-fetoprotein (AFP) and/or des-γ-carboxyprothrombin (DCP).

Patients were asked to give their written informed consent to enter the study, which was approved by the Institutional Review Board of Yamaguchi University Hospital.

Table 1 summarizes the clinical profiles of the 44 HCC patients treated by HAIC. They included 38 men and 6 women, with an average age of 62.3 years (range, 32–79 years). Thirty-two patients were infected with hepatitis C virus (HCV), 11 were infected with hepatitis B virus (HBV), and 1 was not infected with either HCV or HBV. Thirty-five patients had previously undergone treatment for HCC (surgery, percutaneous ethanol injection,[14] percutaneous hot water injection therapy,[15] percutaneous microwave coagulation therapy,[16] percutaneous radiofrequency ablation therapy,[17] transcatheter arterial embolization,[18] or transcatheter arterial chemoembolization[19]). Tumor stage and PVTT grading were determined according to the criteria of the Liver Cancer Study Group of Japan.[20,21] PVTT grading was based on the location of the tumor thrombus in the peripheral portal vein: Vp1, tumor thrombus in a third or more of the peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in the first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein. Tumor staging was done using the Liver Cancer Study Group of Japan criteria, based on the following three conditions (T factor): solitary, <2 cm in diameter, or no vessel invasion. Stage I was defined as fulfilling the three conditions (T1), stage II as fulfilling two of the three conditions (T2), stage III as fulfilling one of the three conditions (T3), stage IV A as fulfilling none of the three conditions (T4) with no distant metastasis or any T factor with lymph node metastasis, and stage IV B as any T factor with distant metastasis.

Technique of catheter placement

A 5-French heparin-coated catheter (Anthron P-U Catheter; Toray Medical, Tokyo, Japan) was inserted intraluminally from the right femoral artery or the subclavian artery with a subcutaneously implanted reservior, and was positioned in the proper or common hepatic artery. The gastroduodenal artery and the right gastric artery were occluded with steel coils as required to prevent gastroduodenal injury from the anticancer agents. The entire procedure was performed with the patient under local anesthesia. To prevent occlusion of the device, it was filled with 5 ml (5000 units) of a heparin solution every 2 weeks.

Chemotherapeutic regimen

Patients received repeated arterial infusions of chemotherapeutic agents via the injection port. Of the 29 patients who received low-dose CDDP, 5-FU, and leucovorin or isovorin, 9 patients received low-dose CDDP, 5-FU, and leucovorin (12 mg/body), 15 received low-dose CDDP, 5-FU, and isovorin (12.5 mg/body), and 5 received low-dose CDDP, 5-FU, and isovorin (6.25 mg/body). One course of chemotherapy consisted of the daily administration of CDDP (10 mg/body, on days 1 to 5) and leucovorin or isovorin (12 mg leucovorin or 12.5 mg or 6.25 mg isovorin, on days 1 to 5) followed by 5-FU (250 mg/body, on days 1 to 5). Days 6 and 7 were rest days. In the 15 patients who received low-dose CDDP and 5-FU, the same regimen was followed, except for the administration of leucovorin or isovorin. In principle, patients were to receive four serial courses of chemotherapy. Both CDDP and 5-FU were administered by a mechanical infusion pump, set at 1 and 5 h, respectively. Either leucovorin or isovorin was administered at 10 min. As an antiemetic, the serotonin antagonist ondansetron hydrochloride was administered intravenously.

Evaluation

Tumor regression was assessed by computed tomography during angiography (CTA)[22] and/or by digital subtraction angiography (DSA) after the initial treatment. The response criteria defined by the Liver Cancer Study Group of Japan were used. Complete response (CR) was defined as disappearance of the tumor and no evidence of new lesions for at least 4 weeks. Partial response (PR) was defined as a greater than 50% decrease in the tumor and no evidence of new lesions for at least 4 weeks. Minor response (MR) was defined as a less than 50% decrease in the tumor and a greater than 25% decrease and no evidence of new lesions for at least 4 weeks. No change (NC) was defined as a less than 25% decrease in the tumor and no evidence of new lesions for at least 4 weeks. Progressive disease (PD) was defined as a greater than 25% increase in the tumor and evidence of new lesions for at least 4 weeks.

Additional therapy

In principle, the treatment course was repeated several times unless the tumor progressed during the therapy. We tried to perform additional therapies, such as microwave coagulation therapy (MCT);[16] percutaneous radiofrequency ablation therapy (RFA);[17] transcatheter arterial chemoembolization (TACE),[19] using epirubicin HCL, mitomycin C, and lipiodol; operation; and chemotherapy, using other drugs (epirubicin HCL, mitomycin C) after evaluation of the effects of this study. Of 20 patients who received additional therapies, 9 patients were responders (CR + PR) and 11 were nonresponders (MR + NC + PD). Of the responders, 2 patients were treated with RFA, 4 were treated with TACE, 2 were treated with RFA and TACE, and 1 was treated with MCT and TACE. Of the nonresponders, 1 patient was treated with MCT, 1 was treated with RFA and operation, 4 were treated with TACE, and 5 were treated with chemotherapy.

Statistical analysis

The data values were expressed as means ± SDs. Statistical analyses were performed using the unpaired *t*-test, and the Mann-Whitney *U*-test as appropriate. Univariate analysis, to identify predictors of survival, was performed by the Kaplan-Meier method[23] and compared by the log-rank test. Thirteen variables were assessed for survival, including sex, age (younger or older than 65 years), the presence of hepatitis-C antibody (HCV-Ab), hepatic reserve capacity (Child-Pugh score A or B[24]), the presence of previous therapy for HCC, AFP level (<1000 or ≧1000 ng/ml), DCP level (<1000 or ≧1000 mAU/ml), maximum tumor size (<50 or ≧50 mm), PVTT rating (Vp0-1 or Vp2-4), tumor stage (stage II, III or stage IV-A, IV-B), therapeutic effect after HAIC (CR, PR or MR, NC, PD), use of leucovorin or isovorin (yes or no), and additional therapy (yes or no). The multivariate analysis was done by the Cox proportional hazards model with stepwise selection. Survival was confirmed up to August 31, 2003. Statistical significance was defined as a P value of less than 0.05.

Results

Response to therapy

Of the 44 patients, 5 (11%), 12 (27%), 2 (5%), 12 (27%), and 13 (30%) patients exhibited CR, PR, MR, NC, and PD, respectively (response rate [patients with CR + PR/all patients], 38%). In the low-dose CDDP and 5-FU with leucovorin/isovorin group (29 patients), 4 (14%), 10 (34.5%), 2 (7%), 10 (34.5%), and 3 (10%) patients exhibited CR, PR, MR, NC, and PD, respectively (response rate, 48.3%). In the low-dose CDDP and 5-FU group (15 patients), 1 (7%), 2 (13%), 0 (0%), 2 (13%), and 10 (67%) patients exhibited CR, PR, MR, NC, and PD, respectively (response rate, 20%). The response rate in the low-dose CDDP and 5-FU with leucovorin/isovorin group was significantly better than that in the low-dose CDDP and 5-FU group ($P = 0.002$; Mann-Whitney *U*-test; Table 2). There were no statisti-

Table 2. Clinical responses to therapy

	CR	PR	MR	NC	PD	Response rate
Low-dose CDDP and 5-FU with leucovorin/isovorin (n = 29)	4	10	2	10	3	48.3% *
Low-dose CDDP and 5-FU (n = 15)	1	2	0	2	10	20% *
Total no. of patients (n = 44)	5	12	2	12	13	38%

*P = 0.002 (Mann-Whitney U-test)
CR, complete response; PR partial response; MR, minor response; NC, no change; PD, progressive disease

Table 3. Clinical characteristics of patients treated with low-dose CDDP and 5-FU with leucovorin/isovorin, or low-dose CDDP and 5-FU

Clinical characteristics	Low-dose CDDP and 5-FU with leucovorin/isovorin (n = 29)	Low-dose CDDP and 5-FU (n = 15)	P value
Sex (male/female)	26/3	12/3	0.376
Age (younger than 65 years/66 years and older)	19/10	9/6	0.718
HCV (+/−)	19/10	13/2	0.135
Child-Pugh (A/B)[a]	19/10	10/5	0.939
Previous treatment (yes/no)	25/4	10/5	0.128
Plasma concentration of AFP (<1000 ng/ml/≧1000 ng/ml)	20/9	4/11	0.008
Plasma concentration of DCP (<1000 mAU/ml/≧1000 mAU/ml)	17/12	10/5	0.603
Maximum tumor size (<50 mm/≧50 mm)	18/11	4/11	0.026
Tumor stage (II/III/IV A/IV B)[b]	6/10/12/1	0/6/7/2	0.141
Grade of portal invasion (Vp 0/1/2/3/4)[c]	16/2/3/3/5	7/1/1/4/2	0.656
Additional therapy (yes/no)	12/17	8/7	0.450

HCV, hepatitis C virus; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin; Vp, portal tumor thrombosis
[a] Child-Pugh stage
[b] According to the Liver Cancer Study Group of Japan
[c] Portal invasion. Vp1, in a third or more of the peripheral branches; Vp2, in the second branch; Vp3, in the first branch; Vp4, in the trunk

cally significant differences in the clinical characteristics between the two groups, except for AFP level and maximum tumor size (Table 3).

Survival and prognostic factors

The cumulative survival rates of the 44 patients are shown in Fig. 1. The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates were 39%, 18%, 12%, 9%, and 9%. The median survival duration of the 44 patients treated with HAIC was 9.4 months (range, 1.9–68.5 months). The cumulative survival rates of patients treated with low-dose CDDP and 5-FU with leucovorin/isovorin, or low-dose CDDP and 5-FU, are shown in Fig. 2. The regimen using low-dose CDDP and 5-FU with leucovorin/isovorin tended to improve survival rates, although there was no significant difference between the two groups (P = 0.097).

Three of the 13 factors analyzed by univariate analysis showed prognostic significance—the Child-Pugh score (P = 0.013), AFP level (P = 0.010), and therapeutic effect after HAIC (P = 0.003; Table 4). The cumulative survival rates of patients by Child-Pugh score, AFP levels, and therapeutic effect after HAIC are shown in

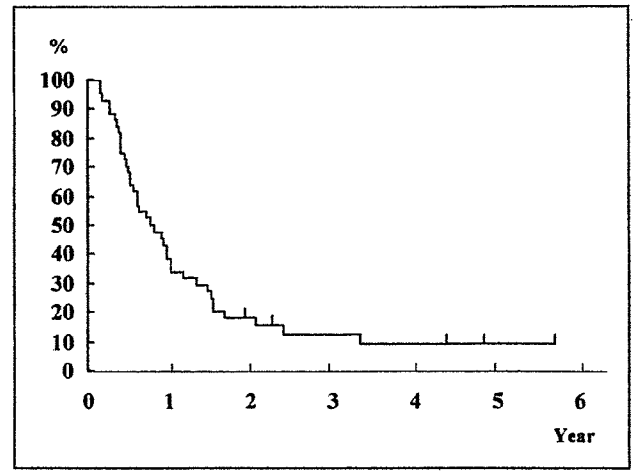

Fig. 1. Cumulative survival of 44 patients with advanced hepatocellular carcinoma treated with hepatic arterial infusion chemotherapy. The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates were 39%, 18%, 12%, 9%, and 9%, respectively

Table 4. Factors influencing cumulative survival of patients: univariate analysis

Factors	*P* value
Sex (male/female)	0.873
Age (younger than 65 years/66 years and older)	0.872
HCV (+/−)	0.439
Child-Pugh (A/B)[a]	0.013
Previous treatment (yes/no)	0.942
Plasma concentration of AFP (<1000 ng/ml/≧1000 ng/ml)	0.010
Plasma concentration of DCP (<1000 mAU/ml/≧1000 mAU/ml)	0.354
Maximum tumor size (<50 mm/≧50 mm)	0.732
Tumor stage (II/III/IV A/IV B)[b]	0.288
Grade of portal invasion (Vp 0–1/Vp 2–4)[c]	0.622
Therapeutic effect (CR or PR/MR, NC, or PD)	0.003
Leucovorin or isovorin (yes/no)	0.097
Additional therapy (yes/no)	0.107

HCV, hepatitis C virus; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin; Vp, portal tumor thrombosis
[a] Child-Pugh stage
[b] According to the Liver Cancer Study Group of Japan
[c] Portal invasion. Vp1, in a third or more of the peripheral branches; Vp2, in the second branch; Vp3, in the first branch; Vp4, in the trunk

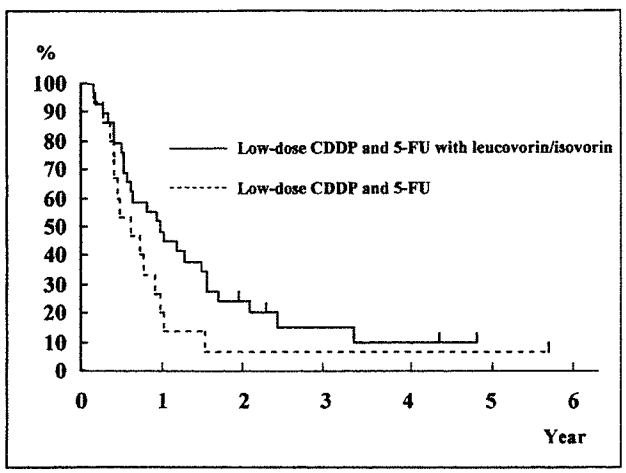

Fig. 2. Cumulative survival rates are shown for patients treated with low-dose cisplatin (*CDDP*) and 5-fluorouracil (*5-FU*) with leucovorin/isovorin, or low-dose CDDP and 5-FU. The 1-, 2-, 3-, and 4-year cumulative survival rates for low-dose CDDP and 5-FU with leucovorin/isovorin were 48%, 24%, 15%, and 10%, respectively. The median survival duration was 11.8 months. The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates for low-dose CDDP and 5-FU were 20%, 7%, 7%, 7%, and 7%, respectively. The median survival duration was 7.3 months. There was no significant difference between the two groups ($P = 0.097$)

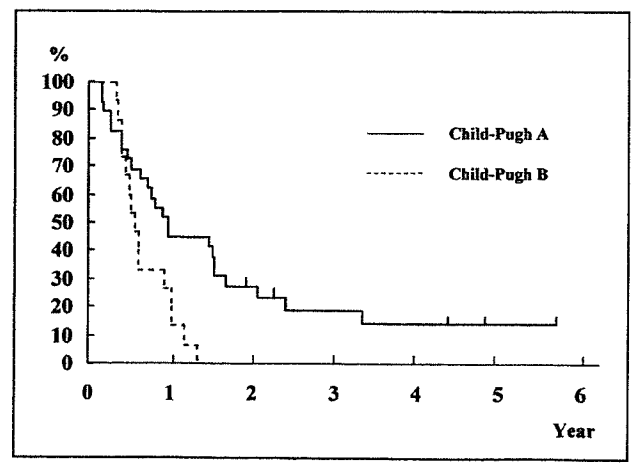

Fig. 3. Cumulative survival rates of patients by Child-Pugh score are shown. For patients with Child-Pugh A score, the 1-, 2-, 3-, 4-, and 5-year cumulative survival rates were 45%, 28%, 19%, 14%, and 14%, respectively. The median survival duration was 11.6 months. For those with Child-Pugh B score, the 1- and 2-year cumulative survival rates were 27% and 0%, respectively. The median survival duration was 6.7 months. There was a significant difference between the two groups (P 0.013)

Figs. 3, 4, and 5, respectively. Multivariate analysis showed the same variables—the Child-Pugh score ($P = 0.018$), AFP level ($P = 0.009$), and therapeutic effect after HAIC ($P = 0.01$), to be independent predictors of mortality (Table 5).

Causes of death

Five patients remained alive throughout the entire observation period, and 39 patients died. Thirty patients (77%) died of cancer-related disease. Of these, 28 died of tumor extension and 2 died of tumor rupture. Four patients (10%) died of gastrointestinal bleeding and 3 (8%) died of liver failure. Two patients (5%) died of pneumonia.

Table 5. Factors influencing cumulative survival of patients: multivariate analysis

Factors	Hazard ratio	95% CI	*P* value*
Child-Pugh (A/B)	2.474	1.168–5.242	0.018
Plasma concentration of AFP (<1000 ng/ml/≧1000 ng/ml)	2.492	1.251–4.965	0.009
Therapeutic effect (CR or PR/MR, NC, or PD)	2.614	1.259–5.430	0.01

*Cox proportional hazards model with stepwise selection
AFP, α-fetoprotein; CI, confidence interval

Table 6. Causes of death

	Low-dose CDDP and 5-FU with leucovorin/isovorin (*n* = 29)	Low-dose CDDP and 5-FU (*n* = 15)	Total no. of patients (*n* = 44)
Alive	4 (CR, 2; PR, 1; NC, 1)	1 (CR, 1)	5
Dead	25 (CR, 2; PR, 9; MR, 2; NC, 9; PD, 3)	14 (PR, 2; NC; 2, PD, 10)	39
Cancer-related disease	18 (CR, 2; PR, 5; MR, 1; NC, 7; PD, 3)	12 (PR, 1; NC, 1; PD, 10)	30 (77%)
Primary cancer-related	15 (PR, 4; MR, 1; NC, 7; PD, 3)	12 (PR, 1; NC, 1; PD, 10)	
Metastatic cancer-related	3 (CR, 2; PR, 1)	0	
Gastrointestinal bleeding	3 (PR, 1; NC, 1; MR, 1)	1 (NC, 1)	4 (10%)
Liver failure	2 (PR, 1; NC, 1)	1 (PR, 1)	3 (8%)
Pneumonia	2 (PR, 2)	0	2 (5%)

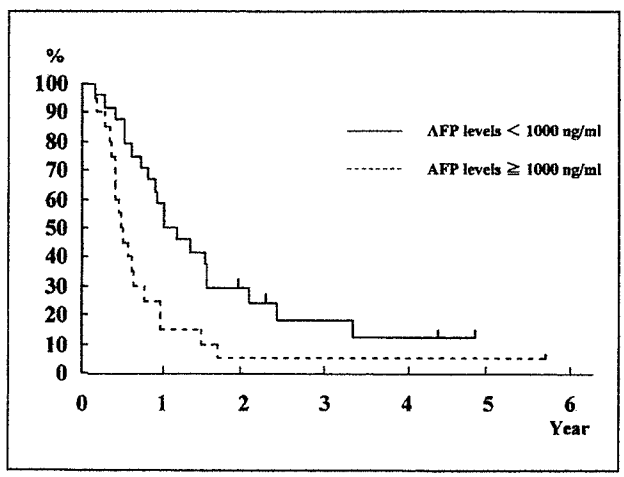

Fig. 4. Cumulative survival rates of patients by α-fetoprotein (*AFP*) level are shown. For patients with an AFP level of less than 1000 ng/ml, the 1-, 2-, 3-, and 4-year cumulative survival rates were 58%, 29%, 19%, 18%, and 12%, respectively. The median survival duration was 12.3 months. For those with an AFP level of 1000 ng/ml or more, the 1-, 2-, 3-, 4-, and 5-year cumulative survival rates were 15%, 5%, 5%, 5% and 5%, respectively. The survival duration was 5.8 months. There was a significant difference between the two groups ($P = 0.010$)

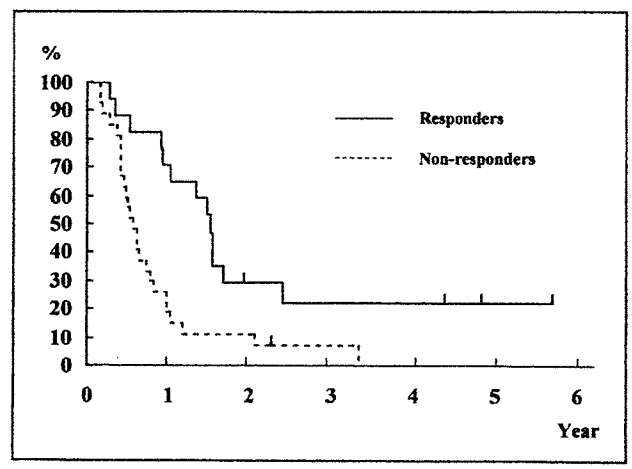

Fig. 5. Cumulative survival rates of patients by therapeutic effect after hepatic arterial infusion chemotherapy (HAIC) are shown. The 1-, 2-, 3-, 4-, and 5-year cumulative survival rates of responders (complete response [CR] + partial response [PR]) were 71%, 29%, 22%, 22%, and 22%, respectively. The median survival duration was 18.4 months. The 1-, 2-, and 3-year cumulative survival rates of non-responders were 19%, 11%, and 7%, respectively. The median survival duration was 6.7 months. There was a significant difference between the two groups ($P = 0.003$)

We compared causes of death between the low-dose CDDP and 5-FU with leucovorin/isovorin group and the low-dose CDDP and 5-FU group (Table 6). In the low-dose CDDP and 5-FU with leucovorin/isovorin group, 4 patients remained alive and 25 died. Of the 4 patients who were alive, 2 had CR; 1, PR; and 1, NC after HAIC. Eighteen patients (72%) died of cancer-related disease. Of these patients, 15 died of primary cancer-related disease and 3 of metastatic cancer-related disease. Of the 15 patients who died of primary

cancer-related disease, 4 had PR; 1, MR; 7, NC; and 3, PD after HAIC. Of the 3 patients who died of metastatic cancer-related disease, 2 had CR and 1, PR. Three patients (12%) died of gastrointestinal bleeding. Of these 3, 1 had PR; 1, NC; and 1, MR. Of the 2 patients (8%) who died of liver failure, 1 had PR and 1, NC. Two patients (8%) with PR after HAIC died of pneumonia.

In the low-dose CDDP and 5-FU group, 1 patient was still alive and 14 patients had died. The surviving patient had CR after HAIC. Twelve patients (86%) died of primary cancer-related disease but none died of metastatic cancer-related disease. Of these 12 patients, 1 had PR; 1, NC; and 10, PD after HAIC. One patient (7%) who had NC after HAIC died of gastrointestinal bleeding. One patient (7%) with PR died of liver failure.

Discussion

The prognosis of advanced HCC remains poor, especially for patients with PVTT.[1-4] Recently, progress in implantable drug delivery systems has made possible the repeated arterial infusion of chemotherapeutic agents for patients with advanced HCC.

We previously designed a new regimen using CDDP, 5-FU, and leucovorin.[12] CDDP and leucovorin can amplify the effect of 5-FU.[9-11,25,26] We thought that they acted as double biochemical modulators for 5-FU. In a randomized study, we demonstrated the efficacy of our regimen, although we investigated only a small number of patients. The response rate for low-dose CDDP and 5-FU with leucovorin was significantly better than that for low-dose CDDP and 5-FU (56% vs 20%; $P = 0.022$). In addition, survival with low-dose CDDP and 5-FU with leucovorin was significantly better than that with low-dose CDDP and 5-FU ($P = 0.033$). We also investigated the efficacy of our regimen with high-dose leucovorin (about two times as much as the previous dose), using isovorin, which is an active form of leucovorin.[13] We reported that there were no significant differences in the response rate (56% vs 53%; $P = 0.71$) and the survival rate ($P = 0.29$) between low-dose leucovorin and high-dose leucovorin. After these studies, we have used a dose of isovorin of 6.25 mg per day in our regimen.

Hepatic arterial infusion chemotherapy (HAIC) is useful for patients with advanced HCC.[4-8] However, little has been established regarding the prognostic factors after HAIC.[27] In the current study, we investigated the factors that influenced survival by applying univariate and multivariate analyses to the 44 patients with advanced HCC treated with HAIC using low-dose CDDP and 5-FU with/without leucovorin (or isovorin).

Univariate analysis demonstrated that three factors; namely, the Child-Pugh score ($P = 0.013$), AFP level ($P = 0.010$), and therapeutic effect after HAIC ($P = 0.003$), influenced the prognosis (Table 4). However, the grade of portal invasion did not influence the prognosis ($P = 0.622$). Although previous studies have documented that PVTT is an important prognostic factor that influences survival in patients with HCC,[28-30] it was not a prognostic factor in our current study. We think that HAIC changed the prognostic factors of advanced HCC. Ando et al.[27] reported the efficacy of HAIC using low-dose CDDP and 5-FU for 48 patients having advanced HCC with PVTT. In their study, the therapeutic effect and hepatic reserve capacity (Child classification[31]) were identified as significant prognostic factors by univariate analysis, and multivariate analysis identified only the therapeutic effect as being significantly related to survival. Our study demonstrated by multivariate analysis that the Child-Pugh score ($P = 0.018$), AFP level ($P = 0.009$), and therapeutic effect after HAIC ($P = 0.01$) were significant prognostic factors, as they were on univariate analysis. Except for the AFP level, our results were the same as those in the report by Ando et al.[27] Previous reports have demonstrated that AFP is one of the prognostic factors in patients with HCC.[32-35] The importance of the AFP level as a prognostic factor for HCC has been shown in a report from the Center of the Liver Italian Program (CLIP) investigators.[2] Hanazaki et al.[36] reported, similarly to our result, that an AFP value of 1000 ng/ml or more was an independent unfavorable factor affecting survival after hepatic resection for HCC with hepatitis C virus infection. On the other hand, DCP and the grade of portal invasion were not prognostic factors in our univariate analysis in the present study ($P = 0.354$, $P = 0.622$). Koike et al.[37] have reported that DCP is a useful factor indicating a predisposition for the development of portal venous invasion. Therefore, AFP may influence the tumor characteristics of HCC, differing from DCP, which is related to portal venous invasion. We consider that AFP may be a useful parameter for determining survival when advanced HCC is treated with HAIC. Recently, AFP L3 was reported to be a useful prognostic factor in patients with HCC.[38,39] Although we did not measure AFP L3 in our study, we think that further investigation of it is required to determine its usefulness as a prognostic factor in patients with advanced HCC receiving HAIC.

The regimen using low-dose CDDP and 5-FU with leucovorin/isovorin tended to improve survival rates, although there was no significant difference between the groups with our two regimens ($P = 0.097$). However, four patients who had PR after HAIC with low-dose CDDP and 5-FU with leucovorin/isovorin died: gastrointestinal bleeding (1 patient; survival period, 4.1

months), hepatic failure (1 patient; survival period, 11.4 months), and pneumonia (2 patients; survival periods, 3.2 months and 6.4 months). We think that the reason why there was no significant difference in the survival between the two groups was the short survival periods of the four patients. Although there were only slight differences in the clinical characteristics between the two groups, the response rate in the low-dose CDDP and 5-FU with leucovorin/isovorin group was significantly better than that in the low-dose CDDP and 5-FU group ($P = 0.002$). Therefore, low-dose CDDP and 5-FU with the addition of a biochemical modulator appears to be a useful regimen for advanced HCC.

Ando et al.[27] reported that additional therapy following HAIC might be an option for prolongation of survival. In our study, additional therapy tended to improve survival rates, although it was not a significant prognostic factor on univariate analysis ($P = 0.107$). However, additional therapy following HAIC may be found to be a significant prognostic factor in studies with a large number of patients with advanced HCC.

In conclusion, patients who had advanced HCC with favorable hepatic reserve capacity and lower AFP level were suitable candidates for HAIC. Moreover, the regimen using low-dose CDDP and 5-FU with leucovorin/isovorin may be suitable for advanced HCC patients because of the improvement in the response rate and survival compared with the low-dose CDDP and 5-FU regimen without leucovorin/isovorin.

References

1. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918–28.
2. The Cancer of the Liver Italian Program (CLIP) investigators. A new prognostic system for patients with hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology 1998;28: 751–5.
3. Leung TW, Tang AM, Zee B, Yu SC, Lai PB, Lau WY, et al. Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. Cancer 2002;94:421–7.
4. Chung YH, Song H, Song BC, Lee GC, Koh MS, Yoon HK, et al. Combined therapy consisting of intraarterial cisplatin infusion and systemic interferon-α for hepatocellular carcinoma patients with major portal vein thrombosis or distant metastasis. Cancer 2000;88:1986–91.
5. Toyada H, Nakano S, Kumada T, Takeda I, Sugiyama K, Osada T, et al. The efficacy of continuous local arterial infusion of 5-fluorouracil and cisplatin through an implanted reservoir for severe advanced hepatocellular carcinomas. Oncology 1995;52: 295–9.
6. Ando E, Yamashita F, Tanaka M, Tanigawa K. A novel chemotherapy for advanced hepatocellular carcinoma with tumor thrombosis of the main trunk of the portal vein. Cancer 1997;79: 1890–6.
7. Urabe T, Kaneko S, Matsusuta E, Unoura M, Kobayashi K. Clinical pilot study of intrahepatic arterial chemotherapy with methotrexate, 5-fluorouracil, cisplatin and subcutaneous interferon-alpha-2b for patients with locally advanced hepatocellular carcinoma. Oncology 1998;55:39–47.
8. Sakon M, Nagano H, Dono K, Nakamori S, Umeshita K, Yamaka A, et al. Combined intraarterial 5-fluorouracil and subcutaneous interferon-α therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. Cancer 2002;94:435–42.
9. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectral cancer. Cancer 1989;63: 1026–30.
10. Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, et al. Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 1989;7: 1407–17.
11. Buroker TR, O'Connell MJ, Wieand HS, Krook JE, Gerstner JB, Mailliard JA, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. J Clin Oncol 1994;12:12–20.
12. Yamasaki T, Kurokawa F, Shirahashi H, Kusano N, Hironaka K, Masuhara M, et al. Novel arterial infusion chemotherapy using cisplatin, 5-fluorouracil, and leucovorin for patients with advanced hepatocellular carcinoma. Hepatol Res 2002;23:7–17.
13. Yamasaki T, Kurokawa F, Takami T, Omori K, Kawaguchi K, Tsuchiya M, et al. Arterial infusion chemotherapy using cisplatin, 5-fluorouracil, and isovorin for patients with advanced hepatocellular carcinoma, pilot study: is a high dose of the biochemical modulator effective? Hepatol Res 2003;27:36–44.
14. Ebara M, Ohoto M, Sugiura N, Kita K, Yoshikawa M, Okuda K, et al. Percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Study of 95 patients. J Gastroenterol Hepatol 1990;5:616–26.
15. Yamasaki T, Matsuzaki Y, Irie S, Terai S, Yamashita A, Kurokawa F, et al. Percutaneous hot water injection therapy (PHoT) for treatment of hepatocellular carcinoma: a comparison with percutaneous ethanol injection therapy (PEIT). Int Hepatol Commun 1995;3:305–9.
16. Seki T, Wakabayashi M, Nakagawa T, Itho T, Shiro T, Kunieda K, et al. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. Cancer 1994;74: 817–25.
17. Yamasaki T, Kurokawa F, Shirahashi H, Kusano N, Hironaka K, Okita K. Percutaneous radiofrequency ablation therapy with combined angiography and computed tomography assistance for patients with hepatocellular carcinoma. Cancer 2001;91:1342–8.
18. Matsui O, Kadoya M, Yoshikawa J, Gabata T, Arai K, Demachi H, et al. Small hepatocellular carcinoma: treatment with subsegmental transcatheter arterial embolization. Radiology 1993;188: 79–83.
19. Sakurai M, Okamura J, Kuroda C. Transcatheter chemoembolization effective for treating hepatocellular carcinoma: a histopathologic study. Cancer 1984;54:387–92.
20. Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer (in Japanese). 4th ed. Tokyo: Kanehara; 2000. p. 19.
21. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003;38:207–15.
22. Kanematsu M, Hoshi H, Imaeda T, Murakami T, Inaba Y, Yokoyama R, et al. Detection and characterization of hepatic tumors: value of combined helical CT hepatic arteriography and CT during arterial portography. Am J Roentgenol 1997;168:1193–8.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–81.

24. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.
25. Scanlon KJ, Newman EM, Lu Y, Priest DG. Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. Proc Natl Acad Sci U S A 1986;83:8923–5.
26. LoRusso P, Pazdur R, Redman BG, Kinzie J, Vaitkevicius V. Low-dose continuous infusion 5-fluorouracil and cisplatin: phase II evaluation in advanced colorectal carcinoma. Am J Clin Oncol 1989;12:486–90.
27. Ando E, Tanaka M, Yamashita F, Kuromatsu R, Yutani S, Fukumori K, et al. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer 2002;95:588–95.
28. The Liver Cancer Study Group of Japan. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. Ann Surg 1990;211:277–87.
29. Okada S, Okazaki N, Nose H, Yoshimori M, Aoki K. Prognostic factors in patients with hepatocellular carcinoma receiving systemic chemotherapy. Hepatology 1992;16:112–7.
30. Fujii T, Takayasu K, Muramatsu Y, Moriyama N, Wakao F, Kosuge T, et al. Hepatocellular carcinoma with portal tumor thrombus: analysis of factors determining prognosis. Jpn J Clin Oncol 1993;23:105–9.
31. Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, editor. The liver and portal hypertension. Philadelphia: Saunders; 1964:49–51.
32. Nomura F, Ohnishi K, Tanabe Y. Clinical features and prognosis of hepatocellular carcinoma with reference to serum alpha-fetoprotein levels. Analysis of 606 patients. Cancer 1989;64:1700–7.
33. Yamashita Y, Takahashi M, Koga Y, Saito R, Nanakawa S, Hatanaka Y, et al. Prognostic factors in the treatment of hepatocellular carcinoma with transcatheter arterial embolization and arterial infusion. Cancer 1991;6:385–91.
34. Izumi R, Shimizu K, Kiriyama M, Hashimoto T, Urade M, Yagi M, et al. Alpha-fetoprotein production by hepatocellular carcinoma is prognostic of poor patient survival. J Surg Oncol 1992; 49:151–5.
35. Pompili M, Rapaccini GL, Covino M, Pignataro G, Caturelli E, Siena DA, et al. Prognostic factors for survival in patients with compensated cirrhosis and small hepatocellular carcinoma after percutaneous ethanol injection therapy. Cancer 2001;92:126–35.
36. Hanazaki K, Kajikawa S, Koide N, Adachi W, Amano J. Prognostic factors after hepatic resection for hepatocellular carcinoma with hepatitis C viral infection: univariate and multivariate analysis. Am J Gastroenterol 2001;96:1243–50.
37. Koike Y, Shiratori Y, Sato S, Obi S, Teratani T, Imamura M, et al. Des-γ-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma. A prospective analysis of 227 patients. Cancer 2001;91:561–9.
38. Aoyagi Y, Isokawa O, Suda T, Watanabe M, Suzuki Y, Asakura H. The fucosylation index of alpha-fetoprotein as a possible prognostic indicator for patients with hepatocellular carcinoma. Cancer 1998;83:2076–82.
39. Aoyagi Y, Mita Y, Suda T, Kawai K, Kuroiwa T, Igarashi M, et al. The fucosylation index of serum alpha-fetoprotein as a useful prognostic factor in patients with hepatocellular carcinoma in special reference to chronological changes. Hepatol Res 2002;23: 287–95.

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Percutaneous radiofrequency ablation with cooled electrodes combined with hepatic arterial balloon occlusion in hepatocellular carcinoma

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Background. We have reported that percutaneous radiofrequency ablation (RFA) with balloon occlusion of the hepatic artery (balloon-occluded RFA), using an expandable electrode, increases the coagulation area. In this study, we investigated the efficacy of balloon-occluded RFA and balloon-microcatheter-occluded RFA, using a cool RF single electrode. ***Methods.*** We studies 41 patients with 47 hepatocellular carcinoma (HCC) lesions. We treated 28 patients (32 nodules) with balloon-occluded RFA, 5 patients (6 nodules) with balloon-microcatheter-occluded RFA, and 8 patients (9 nodules) with standard RFA. Initial therapeutic efficacy was evaluated with dynamic computed tomography performed 1 week after one session of treatment. ***Results.*** One session of treatment was done for 20 nodules (62.5%) in the balloon-occluded RFA group and for 4 nodules (66.7%) in the balloon-microcatheter-occluded RFA group. We compared the coagulation diameter for balloon-occluded RFA (7 nodules), balloon-microcatheter-occluded RFA (6 nodules), and standard RFA (9 nodules) after one application cycle (12 min). The greatest dimension of the area coagulated by balloon-occluded RFA was significantly larger (greatest long-axis dimension, 47.6 ± 7.8 mm; greatest short-axis dimension, 33.4 ± 7.5 mm) than that coagulated by standard RFA (greatest long-axis dimension, 35.3 ± 4.7 mm; greatest short-axis dimension, 25.9 ± 3.7 mm; $P = 0.002$ for greatest long-axis dimension; $P = 0.041$ for greatest short-axis dimension). However, there was significant difference only in the greatest short-axis dimension of the area coagulated comparing balloon-microcatheter-occluded RFA and standard RFA. ***Conclusions.*** We consider balloon-occluded RFA using a cool RF electrode to be superior to standard RFA for the treatment of HCC, especially when larger coagulation volumes are required.

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Key words: hepatocellular carcinoma, radiofrequency ablation, balloon occlusion, percutaneous local treatment

Introduction

Radiofrequency ablation (RFA), a new technique for the destruction of hepatic tumors, has been reported previously.[1–8] Recently, RFA has been performed as a percutaneous local treatment for hepatocellular carcinoma (HCC) in Japan.[9–11] There are three types of RFA systems used in Japan: the RITA 500PA (RITA Medical Systems, Mountain Views CA, USA) Cool-tip RF (Radionics, Burlington, MA, USA), and RF 2000 (RadioTherapeutic, Sunnyvale, CA, USA) Previous studies have documented necrotic areas of up to 26.7 mm, using the RITA 500PA and an expandable electrode from the some manufacturer (Model 30).[12] A necrotic area of up to 30 cm in diameter produced with a cool RF single electrode has been observed in tumors,[6] and cluster electrodes achieve a much larger necrotic area.[5,8,13] However, the limited volume of coagulation necrosis obtained with each activation of the RF system, and the sometimes irregular burn shape, due to the proximity of large vessels that have a cooling effect, have thus far limited the therapeutic efficacy of RFA for the treatment of HCC.[14] Therefore, we designed an RFA procedure with balloon occlusion of the hepatic artery (balloon-occluded RFA), and we have also reported that balloon-occluded RFA using an expandable electrode increases the area of coagulation necrosis.[9,12] However, our procedure can be performed equally well using other RF systems.

In this study, we investigated the efficacy of balloon-occluded RFA using a cool RF single electrode. In addition, as we do not always succeed with this technique because of variant vascular anatomy or irregular shape

of the hepatic artery, we designed an RFA procedure with balloon microcatheter occlusion of the hepatic artery (balloon-microcatheter-occluded RFA) and decided to undertake a study to evaluate the efficacy of this new technique.

Patients, materials, and methods

Patients

We retrospectively studies 41 patients with 47 HCC lesions. They were admitted to the Department of Gastroenterology and Hepatology, Yamaguchi University School of Medicine, between July 2001 and December 2002. Clinical characteristics of the patients are shown in Table 1.

Of these patients, 28 (32 nodules) were treated with balloon-occluded RFA, 5 (6 nodules) were treated with balloon-microcatheter-occluded RFA, and 8 (9 nodules) were treated with standard RFA. We die not perform RFA with artificial pleural effusion,[15] because HCC lesions located in the hepatic dome were well-visualized by ultrasonography. The diagnosis of HCC was made by imaging studies and/or histological findings, and was based on elevated serum levels of α-fetoprotein (AFP) and/or des-γ-carboxy-prothrombin (DCP).

In the balloon-occluded RFA group, 10 patients (10 nodules) had not received previous treatment for HCC and 18 patients (22 nodules) had previously undergone treatment for HCC. In the 18 patients who had previously undergone treatment for HCC, 21 of the 22 nodules were recurrent intrahepatic nodules, and 1 nodule was at the margin of the treatment area and recurred 6 months after RFA. Nine nodules (9 patients) measured more than 3 cm in diameter. The average tumor size was 25.8 mm and the largest size was 53 mm.

In the balloon-microcatheter-occluded RFA group, three patients (four nodules) had not received previous treatment for HCC, and two patients (two nodules) had previously undergone treatment for HCC. Of the two patients who had previously undergone treatment for HCC, one had a recurrent intrahepatic nodule, and the other had a recurrent nodule at the margin of the treatment area 9 months after RFA. All nodules in this group measured less than 3 cm in diameter. The average tumor size was 19.2 mm and the largest size was 28 mm.

In the standard RFA group, seven patients (eight nodules) had not received previous treatment for HCC. The eighth patient (one nodule) had previously undergone treatment for HCC, and had a recurrent intrahepatic nodule. All nodules measured less than 3 cm in diameter. The average tumor size was 12.8 mm and the larges size was 16 mm.

The underlying liver disease was classified as Child-Pugh class[16] A, B, or C. Patients were asked to give their written informed consent to enter the study, which was approved by the Institutional Review Board of Yamaguchi University Hospital.

Techniques

RF system

The Cool-tip RF system produced radiofrequency waves with a frequency of 480 kHz and a maximum output power of 200 W. Circuitry in the generator allowed continuous monitoring of impedance between the active part of the cooled electrode and the grounding pads placed on the patient's thigh. A 20-cm-long, 17-gauge, cool-tip RF electrode, with a 3-cm-long (CT-2030) or a 2-cm-long (CT-2020) exposed metallic tip was used to deliver RF energy. Two patients who received balloon-occluded RFA were treated using the CT-2020, and the other patients were treated using the CT-2030. During lesion ablation, a thermocouple embedded in the electrode tip continuously measured the local temperature, and the maximum radiofrequency

Table 1. Clinical characteristics of patients with hepatocellular carcinoma (HCC) treated by balloon-occluded radiofrequency ablation (RFA), balloon-microcatheter-occluded RFA, or standard RFA

Clinical characteristics	Balloon-occluded RFA (*n* 28; 32 nodules)	Balloon-microcatheter-occluded RFA (*n* 5; 6 nodules)	Standard RFA (*n* 8; 9 nodules)
Sex (male/female)	22/6	3/2	3/5
Age (years)[a]	66.7 ± 9.2	70.6 ± 6.0	67.8 ± 7.0
Child-Pugh (A/B/C)	22/6/0	3/2/0	8/0/0
HCV/HBV/unknown	22/3/3	5/0/0	7/1/0
Tumor size (mm)[a]	25.8 ± 10.8	19.2 ± 5.4	12.8 ± 2.4
Initial/previous treatment	10/18	3/2	7/1

HCV, hepatitis C virus; HBV, hepatitis B virus
[a] Data values are expressed as means ± SD

power prevented impedance from rising more than 30 Ω above the baseline value. A peristaltic pump ensured cooling of the electrode with 0°C water at a flow rate sufficient to maintain the temperature of the electrode below 25°C. In principle, RF energy was applied for 12 min (one application cycle). For two nodules treated with balloon-occluded RFA, the application time was only 6 min, because one tumor was located close to the gallbladder and another was located to the liver surface. When necessary, after the first ablation, the electrode was pulled out 1.5 cm, and a second application was started. The application time after the first ablation was 6 min.

In the balloon-occluded RFA group, the tumors were treated with one to three insertions of the electrode per procedure, because the tumor size was larger than that in the other groups. In principle, for each tumor larger than 3 cm in diameter, two to three insertions were planned. One to nine application cycles (range, 6–60 min; mean ± SD, 21 ± 12.9 min) were performed. In the balloon-microcatheter-occluded RFA group and standard RFA group, the tumors were treated with one insertion of the electrode per procedure and one application cycle (12 min).

Balloon-occluded RFA

Catheter placement was done using the Seldinger approach through the femoral artery, with a 5.0-Fr catheter (Clinical Supply, Gifu, Japan). The angiography combined with computed tomography (angio-CT)[17] system used was a Somatom plus 4F (Siemens, Erlagen, Germany). Before treatment, CT during arterial portography (CTAP) and CT arteriography (CTA) were performed. A catheter was placed in the superior mesenteric artery for CTAP and in the common or proper hepatic artery for CTA. CT scanning for CTAP started 30 s after 50 ml of contrast medium (Iomeron 300; Eisai, Tokyo, Japan) diluted with saline (1:1 ratio), was injected at a rate of 2 ml per s. CT scanning for CTA started 5 s after the injection of 15–20 ml of diluted contrast medium, at a rate of 1.5–2 ml per s.

The procedure was performed under real-time Ultrasound (US) guidance (SSD-5500; ALOKA, Tokyo, Japan) with a 3.5-MHz convex probe. First, CTAP and CTA were performed before treatment. Local anesthesia was induced with 5 ml of 0.5% lidocaine. Before treatment, 15 mg pentazocine hydrochloride and 25 mg hydroxyzine hydrochloride were administered intramuscularly, and then 15 mg pentazocine hydrochloride was administered intravenously. In addition, 10–20 mg ketamine hydrochloride, diluted with 100 ml of saline, was administered intravenously for reduction of severe pain. We then performed RFA with balloon occlusion of the proper hepatic artery (balloon-occluded RFA), using a balloon with a 9-mm outer diameter attached to a 5-Fr catheter (Clinical Supply). During interruption of the hepatic arterial flow, the RF generator was activated; 2–3 ml of heparin sodium (10 U/ml) was sometimes administered to prevent thrombosis of the hepatic artery during the occlusion. After treatment, CTA was performed again to evaluate the effect of the procedure (RFA with angio-CT assistance[9]). Patients were instructed to lie quietly in bed for 12 h after treatment.

Balloon-microcatheter-occluded RFA

This technique was performed when we did not succeed with the balloon-occluded RFA because of variant vascular anatomy or irregular shape of the hepatic artery. The procedures for the catheter placement and the angio-CT assistance[9] were same as those described above.

To insert the balloon microcatheter, we exchanged the 5.0-Fr catheter for a 5.1-Fr guiding catheter (Elway; inner diameter, 1.32 mm; Clinical Supply.) We then performed RFA with balloon microcatheter occlusion of the hepatic artery (balloon-microcatheter-occluded RFA). A 10-mm-length balloon, with a 4-mm outer diameter, attached to a Commodore temporary occlusion balloon catheter (Cordis; Johnson and Johnson, USA) and Agility guidewire (Cordis; Johnson and Johnson) were used for occlusion of the right or left hepatic artery (Fig. 1); 0.11 ml of contrast medium diluted with saline (1:3 ratio) was injected into the balloon. During interruption of the hepatic arterial flow, the RF generator was activated.

Assessment of therapeutic efficacy

To examine the initial therapeutic effect, dynamic CT scans were obtained 1 week after treatment. We measured the size of the nonenhanced portion of the liver. Tumor necrosis was considered complete when no areas of enhancement were seen in the tumor or at the periphery on CT scans. If the size of the necrotic area was almost the same as that of the tumor, and CT scans showed partial enhancement of a portion of the tumor, we performed an additional session of standard RFA. A second RF procedure was planned as soon as possible for patients who did not show a complete response after the first procedure. Repeated dynamic CT scans were performed every 3–4 months thereafter.

Overall follow up ranged from 2.8 to 24.8 months (mean ± SD, 15.6 ± 5.5 months). Follow up in the balloon-occluded RFA group was from 2.8 to 24.8 months (mean ± SD, 14.8 ± 5.5 months), that in the balloon-microcatheter-occluded RFA group was from 12.8 to 24.1 months (mean ± SD, 20.1 ± 5.2 months), and that in the standard group was from 9.9 to 22.3 months (mean ± SD, 15.8 ± 4.6 months). α-Fetoprotein

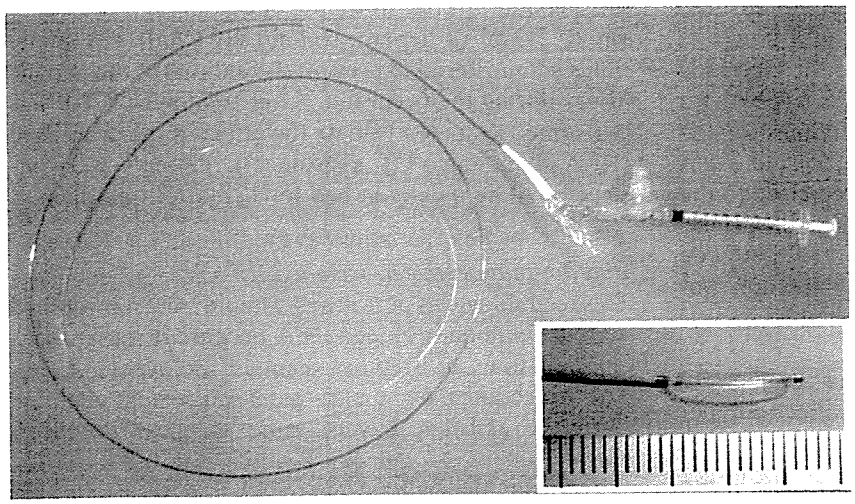

Fig. 1. Balloon microcatheter: Commodore (Cordis; Johnson and Johnson) temporary occlusion balloon catheter; a 10-mm-length balloon, with a 4-mm outer diameter, was attached to a microcatheter

(AFP) and DCP levels were examined before treatment, and 1 month after treatment, and subsequently every 1–2 months.

Balloon-occluded RFA versus standard RFA

We compared the coagulation diameters for balloon-occluded RFA and standard RFA on CT scans 1 week after one application cycle (12 min) in seven patients (seven nodules) treated with balloon-occluded RFA, and eight patients (nine nodules) treated with standard RFA. The CT-2030 was used for all of these patients.

Balloon-microcatheter-occluded RFA versus standard RFA

We compared the coagulation diameters for balloon-microcatheter-occluded RFA and standard RFA on CT scans 1 week after one application cycle (12 min) in the five patients (six nodules) treated with balloon-microcatheter-occluded RFA and the eight patients (nine nodules) treated with standard RFA. The CT-2030 was used for all of these patients.

Statistical analysis

Data values were expressed as means ± SD. Statistical analyses were performed using the unpaired *t*-test. A *P* value of less than 0.05 was considered statistically significant.

Results

Treatment efficacy

In the balloon-occluded RFA group (see Fig. 2 for representative images), the average number of needle insertions was 1.5 ± 0.8. One session of balloon-occluded RFA treatment was done for 20 nodules (62.5%) in 17 patients. Additional sessions of standard RFA were performed for 12 nodules (37.5%) in 11 patients. Thus, the average number of treatment sessions was 1.7 ± 1.1. Nine nodules (9 patients) measured more than 3 cm in diameter. Although the average number of needle insertions in these 9 nodules was 2.1 ± 0.8, combined balloon-occluded RFA and angio-CT assistance[9] techniques could achieve one-session treatment for 4 patients (4 nodules) with large HCC nodules (>3 cm in diameter). During follow up, detection of residual foci of unablated tumors occurred in 2 patients (2 nodules [6%]), at 5 and 8 months after treatment. One patient was treated with balloon-occluded RFA and the other was treated with transcatheter arterial chemoembolization (TACE).

In the balloon-microcatheter-occluded RFA group (Fig. 3), the number of needle insertions was 1. One session of treatment with balloon-microcatheter-occluded RFA was done for four nodules (66.7%) in three patients. Additional sessions of standard RFA were performed for two nodules (33.3%) in two patients. Thus, the average number of treatment sessions was 1.3 ± 0.5. During follow up, there was no detection of residual foci of unablated tumors.

In the standard RFA group, the number of needle insertions was 1. One treatment session of standard RFA was done for eight nodules (88.9%) in seven

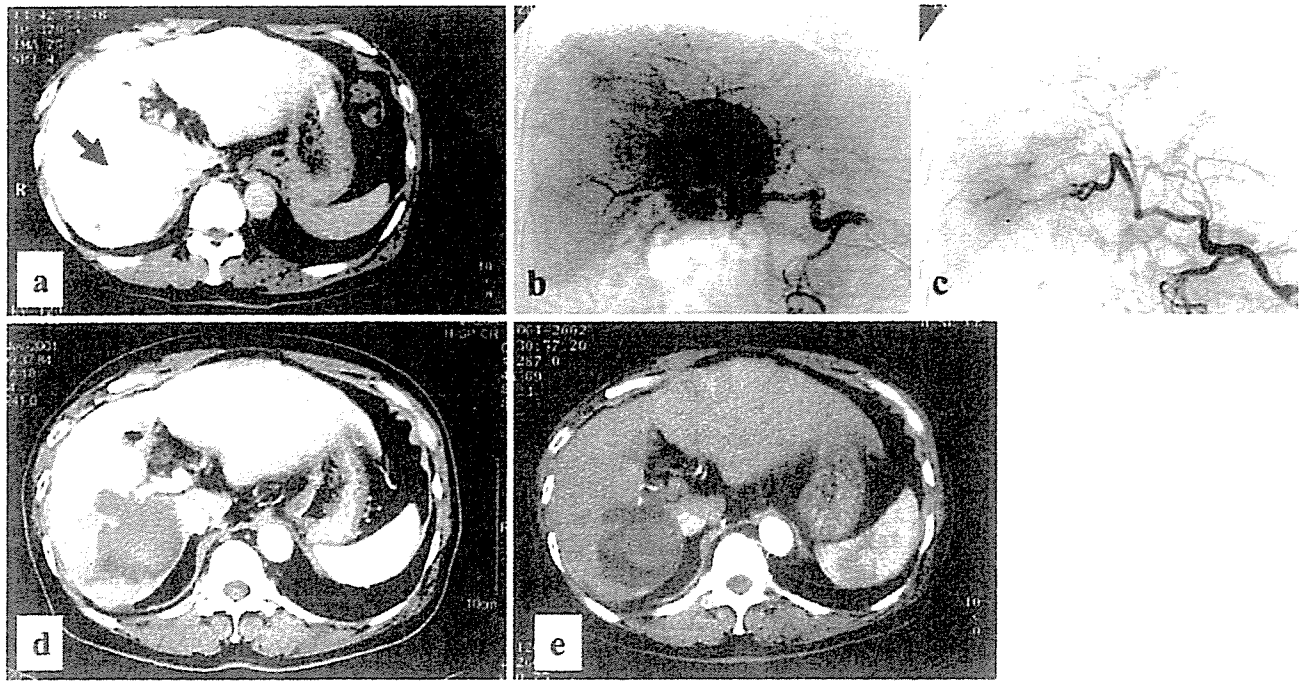

Fig. 2a–e. Balloon-occluded radiofrequency ablation (RFA), using a cool RF single electrode, in a 68-year-old man with a 53-mm-diameter hepatocellular carcinoma in segment 7. **a** Computed tomography arteriography (CTA) before treatment shows a tumor (*arrow*). **b** Digital subtraction angiography (DSA) before treatment shows a tumor stain. **c** We performed balloon-occluded RFA, using a cool RF single electrode (number of needle insertions, 3; total treatment time, 60 min). After treatment, the tumor stain disappearred on DSA. **d** Dynamic CT scan taken 1 week after treatment shows no enhancement in the treated area (85 × 70 mm). **e** Dynamic CT scan taken 1 year after treatment shows no enhancement in the treated area

patients. Additional sessions of standard RFA were performed for one nodule (11.1%) in one patient. Thus, the average number of treatment sessions was 1.1 ± 0.3. During follow up, there was no detection of residual foci of unablated tumors.

During follow up, four patients in the balloon-occluded RFA group died. The cause of death was liver failure in two patients (8.5 months, 18 months) and other causes (encephalitis, aspiration pneumonia) in the other two patients (9.5 months, 2.8 months).

Complications

In the balloon-occluded RFA group, biloma occurred in one patient, hepatic infarction in one patient, and liver abscess in one patient. Biloma and hepatic infarction did not require treatment. Liver abscess was successfully treated with antibiotics. In the balloon-microcatheter-occluded RFA group and the standard RFA group, no severe complications occurred.

Transient increases in the serum aspartate aminotransferase (AST) concentration were observed in all patients. However, 1 week after treatment, the concentration had decreased almost to the pretreatment level.

Balloon-occluded RFA versus standard RFA

The greatest dimension of the area coagulated by balloon-occluded RFA was significantly larger (greatest long-axis dimension, 47.6 ± 7.8 mm; greatest short-axis dimension, 33.4 ± 7.5 mm; $n = 7$ nodules) than that coagulated by standard RFA (greatest long-axis dimension, 35.3 ± 4.7 mm; greatest short-axis dimension, 25.9 ± 3.7 mm; $n = 9$ nodules; $P = 0.002$ for greatest long-axis dimension; $P = 0.041$ for greatest short-axis dimension; Table 2).

Balloon-microcatheter-occluded RFA versus standard RFA

The greatest short-axis dimension of the area coagulated by balloon-microcatheter-occluded RFA was significantly larger (greatest short-axis dimension, 31.5 ± 4.6 mm; $n = 6$ nodules) than that coagulated by standard RFA (greatest short-axis dimension, 25.9 ± 3.7 mm; $n = 9$ nodules; $P = 0.022$; Table 2). However, there was no significant difference between these groups in the greatest long-axis dimension (balloon-microcatheter-occluded RFA, 38.3 ± 5.7 mm; standard RFA, 35.5 ± 4.7 mm; $P = 0.285$; Table 2).

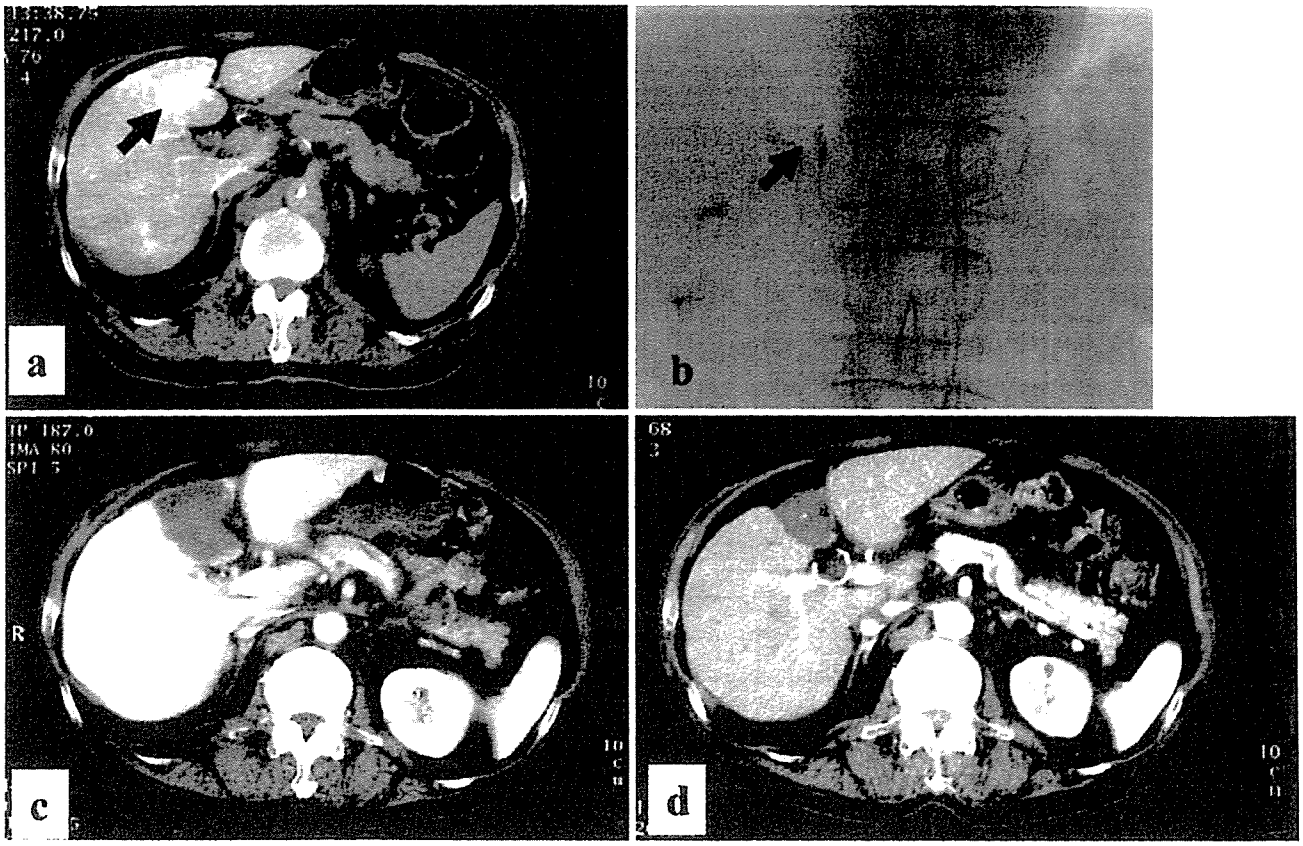

Fig. 3a–d. Balloon-microcatheter-occluded RFA, using a cool RF single electrode, in a 68-year-old man with a 28-mm-diameter hepatocellular carcinoma in segment 4. **a** CTA before treatment shows a tumor (*arrow*). **b** The balloon microcatheter (*arrow*) is placed in the left hepatic artery. We performed balloon-microcatheter-occluded RFA, using a cool RF single electrode (number of needle insertions, 1; treatment time, 12 min). **c** Dynamic CT scan taken 1 week after treatment shows no enhancement in the treated area (43 × 40 mm). **d** Dynamic CT scan taken 1 year after treatment shows no enhancement in the treated area

Table 2. Comparison of balloon-occluded RFA, balloon-microcatheter-occluded RFA, and standard RFA

	Balloon-occluded RFA (n = 7; 7 nodules)	Balloon-microcatheter-occluded RFA (n = 5; 6 nodules)	Standard RFA (n = 8; 9 nodules)
Tumor size	19.6 ± 6.1	19.2 ± 5.4	12.8 ± 2.4
Coagulation area			
Long-axis diameter (mm)	47.6 ± 7.8[1]*	38.3 ± 5.7[3]*	35.3 ± 4.7
Short-axis diameter (mm)	33.4 ± 7.5[2]*	31.5 ± 4.6[4]*	25.9 ± 3.7

[1]*P = 0.002 (vs standard RFA); [2]*P = 0.041 (vs standard RFA); [3]*P = 0.285 (vs standard RFA); [4]*P = 0.022 (vs standard RFA)
Data values are expressed as means ± SD. Student's t-test was used for unpaired data

Discussion

Although radiofrequency ablation (RFA), a new technique for the destruction of hepatic tumors, has been reported previously,[1–8] the limited volume of coagulation necrosis obtained with each activation of the RF system, and the sometimes irregular burn shape due to the proximity of large vessels that have a cooling effect, have thus far limited the therapeutic efficacy of RFA for the treatment of HCC.[14] On the other hand, both animal and clinical studies have suggested that reduction of blood flow can improve tumor ablation efficacy when thermal ablation is used.[14,18–23] To improve the efficacy of PFA, we designed RFA with balloon occlusion of the hepatic artery (balloon-occluded RFA). We have also reported that balloon-occluded RFA increases the area