HCC, and/or death. Exacerbation of liver failure was defined as ascites, hepatic encephalopathy and jaundice. Variceal rupture encompassed both esophageal varices and gastric varices. Patients underwent US every 3 months and new HCC lesions were confirmed using further examinations such as CT, MRI, and angiography. All deaths were recorded regardless of cause.

Patients visited our hospital every 3 months, and were questioned regarding subjective changes experienced during the therapeutic process by the physician in charge of the trial. In addition, each patient underwent a physical examination, blood chemical tests, and US at each observation.

Secondary endpoints were changes in serum T.Bil, AST, Alb, PT, fasting plasma glucose (FPG), and QOL as evaluated using the Short Form (SF)-8 questionnaire.[20,21]

In addition, before and 3 months after RFA treatment, energy metabolism was examined using indirect calorimetry (Deltatrac-II; Datex, Engström, Helsinki, Finland) and changes in non-protein respiratory quotient (npRQ) and oxidative rate of carbohydrates (CHO), protein (PRO) and fat (FAT) were determined.

Protocol

We conducted physical examinations and biochemical tests as an evaluation of background factors before starting the trial. Daily dietary intake was calculated by a dietitian based on a questionnaire regarding the diet of each patient. Thereafter, based on the guidelines of the European Society of Parenteral and Enteral Nutrition (ESPEN),[22] the dietitian checked and maintained a daily dietary intake of 25–35 kcal/kg per day for total energy and 1.0–1.2 g/kg per day for protein every 3 months for one year.

In the BCAA group, Aminoleban EN was administered twice a day (total 100 g/day; 50 g during the daytime and 50 g before bedtime) with a concomitant reduction of 420 kcal for energy and 27 g for protein from the total calorie and protein allowances per day. The dietitian summarized descriptions of the nutritional guidance for daily intake of energy and excess or deficient protein intake in each patient, and this information was provided to the patient via the physician in charge of the trial at each medical institution.

RFA therapy

The Cool-tip Radiofrequency System (Radionics, Burlington, MA, USA) was used for RFA therapy of HCCs. Indications for RFA therapy included both tumor size < 3.0 cm and <3 nodules. RFA therapy was performed once or twice a week until complete necrosis of HCC was confirmed by dynamic CT. Necrosis of HCC was judged as complete when the ablated HCC lesion showed a low-density area in both arterial and portal venous phases with diameter 5.0 mm larger than the pretreatment tumor size. RFA was performed a mean of 1.8 ± 0.7 times in the study subjects.

Statistical analysis

Values are shown as mean ± standard deviation. StatView version 5.0 software (SAS Institute, Cary, NC, USA) was used. Cumulative survival rate was estimated in each group using Kaplan–Meier methods, and differences between groups were analyzed using the log-rank test. With the Wilcoxon signed-rank test, npRQ, changes in oxidative rate of CHO, PRO and FAT, changes in T. Bil, AST, Alb, PT, FPG and changes in SF-8 were analyzed. Moreover, with repeated measures analysis of variance (ANOVA), changes in serum Alb concentration during the trial period were analyzed.

Table 2 Composite endpoint incidence rates after radiofrequency ablation (RFA) therapy

Event	BCAA	Control	*P*
Patient (*n*)	20	15	n.s.
Overall events	2 (10%)	4 (26.7%)	n.s.
Death	1 (5%)	1 (6.7%)	n.s.
Variceal rupture	0 (0%)	1 (6.7%)	n.s.
HCC recurrence	1 (5%)	1 (6.7%)	n.s.
Liver failure†	1 (5%)	3 (20%)	n.s.

†Liver failure: exacerbation of jaundice, ascites, hepatic encephalopathy, and peripheral edema.
BCAA, branched chain amino acid; HCC, hepatocellular carcinoma; n.s., not significant.

Results

Calorie intake

At all observation points during the trial period, more than 75% of patients were taking the full dosage of the BCAA formulation. Total intake of energy and protein during the trial period were 29.5 ± 3.4 kcal/kg per day and 69 ± 10 g/day in the BCAA group, and 29.3 ± 3.3 kcal/kg per day and 67 ± 9 g/day in the control group. No significant differences between groups were identified.

Primary endpoint

A total of six events were recorded during the observation period (Table 2). Two patients died during the trial period (BCAA group, $n = 1$; control group, $n = 1$). A total of two cases (BCAA group, $n = 1$; control group, $n = 1$) developed recurrent HCC. One case in the control group showed rupturing of esophageal varices and four cases (BCAA group, $n = 1$; control group, $n = 3$) displayed exacerbated pathological conditions of liver failure. Frequency of exacerbated liver failure tended to be lower in the BCAA group than in the control group, but no significant difference was observed. The event-free survival curve is shown in Figure 2. Although the event-free survival rate was higher in the BCAA group than in the control group, no significant difference was apparent between groups.

Secondary endpoints

While T. Bil, AST, PT, FPG and BTR exhibited no changes during follow-up, serum Alb increased significantly to 3.25 g/dL over 6 months from 3.18 g/dL before administration in the BCAA group, and subsequently remained at similar levels for 1 year ($P = 0.03$) (Fig. 3, Table 3). In terms of respiratory rate, npRQ increased significantly from 0.81 to 0.86 in the BCAA group ($P < 0.01$). Oxidative rate improved significantly from 25.6% to 43.97% for CHO and from 45.6% to 30.1% for FAT in the BCAA group ($P < 0.01$) (Fig. 4). The oxidative rate of PRO was unchanged after BCAA supplementation. Conversely, the control group exhibited

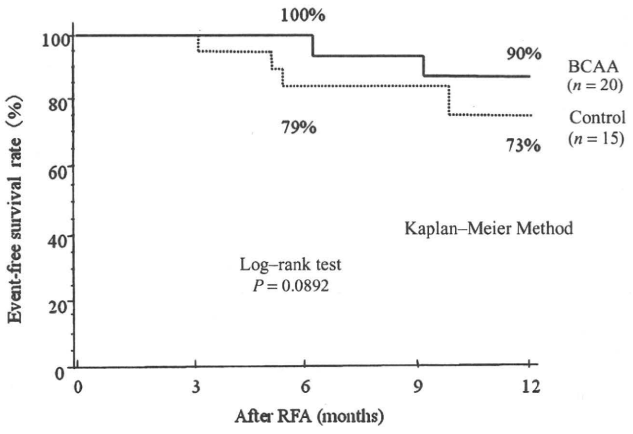

Figure 2 Kaplan–Meier estimates of event-free survival rate after radiofrequency ablation (RFA) in two groups. Events for the primary endpoint include aggravation of hepatic failure, rupture of esophageal or gastric varices, liver cancer recurrence, and death due to liver disease-unrelated causes.

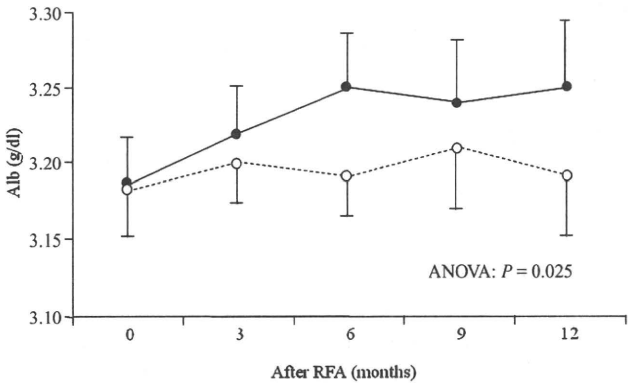

Figure 3 Serial serum albumin levels during 1 year after radiofrequency ablation (RFA) in two groups. Data represent means ± standard error of the mean. —●—, branched-chain amino acid (BCAA) ($n = 20$); -○-, Control ($n = 15$).

no changes in either npRQ or oxidative rates of CHO and FAT. Furthermore, the BCAA group exhibited significant improvements in SF-8 scores for general health (GH), physical functioning (PH), and social functioning (SF) ($P < 0.05$ each) (Fig. 5).

Discussion

Protein-energy malnutrition (PEM) is known to occur frequently in patients with LC and represents an important predictive factor for estimating the prognosis of LC patients with HCC.[23,24] Supplementation with BCAA formula is reportedly useful for improving PEM status and QOL in patients with LC. However, few reports have examined the need for nutritional intervention in patients with HCC undergoing nonsurgical therapies.

Among the nonsurgical therapies, RFA is considered a useful therapy for non-resectable HCC. Due to reliable localized therapeutic effects and safety, RFA is expected to be effective as a curative therapy for small HCC and also as a mass-reduction method for patients awaiting liver transplantation in the United States and other countries.[8–10] However, the majority of HCC patients examined have had LC, and severe complications after RFA therapy have often occurred. Postoperative liver failure has been reported as a complication severe enough to influence the life prognosis of HCC patients.[8,25,26] In addition, due to minor intrahepatic metastases and multicentric carcinogenesis, HCC shows a high rate of repeated recurrence.[11,27,28] Therefore, to improve the long-term prognoses of LC patients with HCC and achieve cancer control, residual liver function must be maintained to prepare for any predicted recurrences.

Our recent study showed that liver function parameters, particularly serum Alb concentration, gradually and dominantly decreased in HCC patients with grade B/C according to the Child-Pugh classification over the course of one year after RFA.[13] Moreover, a score of ≥ 9 points on the Child-Pugh score represented a major risk factor for aggravation of liver function after RFA. These findings were the results in patients without anti-viral therapy.

As shown from these results, the present study first clarified that supplementation with BCAA-enriched nutrients maintained serum Alb levels and improved QOL in patients with HCC as of 1 year after RFA therapy. Recurrence of HCC was observed in one case for each group. Event-free survival rates did not differ

Table 3 Biochemical markers before and 12 months after radiofrequency ablation (RFA) therapy

	BCAA		Control	
	Pre	12 months	Pre	12 months
T. Bil (mg/dL)	1.18 ± 0.6	1.19 ± 0.51	1.16 ± 0.46	1.18 ± 0.43
AST (IU/L)	54.3 ± 30.8	59.2 ± 34.2	58.8 ± 36.9	60.8 ± 40.7
Alb (g/dL)	3.19 ± 0.21	3.25 ± 0.31*	3.18 ± 0.21	3.19 ± 0.35
PT (%)	92.2 ± 3.6	91 ± 5.5	90.1 ± 3.5	89.1 ± 7.5
FPG (mg/dL)	82.2 ± 39.1	87.3 ± 39.7	85.6 ± 41.3	82.9 ± 36.9
BTR	3.35 ± 0.9	3.39 ± 1.2	3.31 ± 1.1	3.31 ± 1.2

Note. These values represent mean ± SD.

*$P = 0.025$, 12 months after RFA versus before RFA in the BCAA group.

12 months, 12 months after RFA therapy; Alb, albumin; AST, aspartate aminotransferase; BCAA, branched-chain amino acid; BTR, branched chain amino acids and tyrosine ratio; FPG, fasting plasma glucose; Pre, before RFA therapy; PT, prothrombin time; T. Bil, total bilirubin.

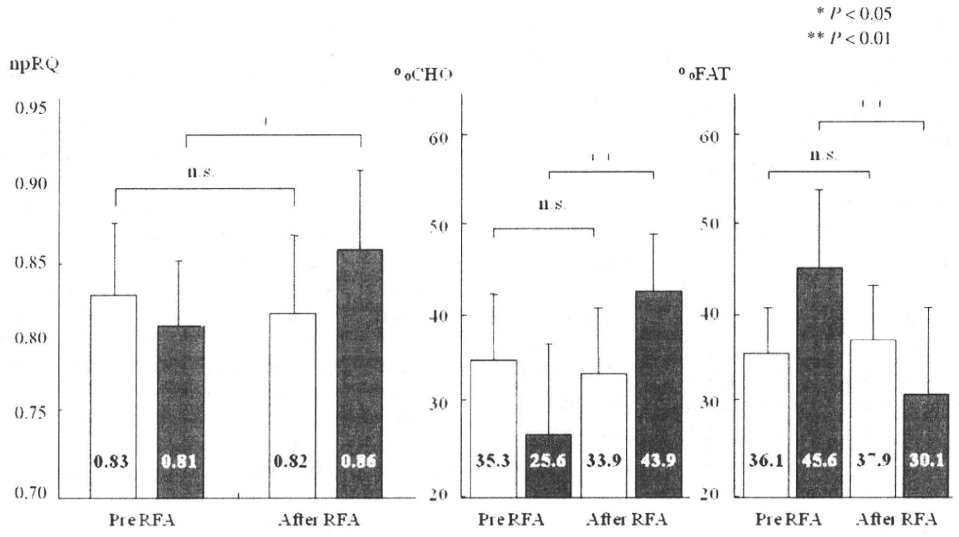

Figure 4 Values of non-protein respiratory quotient (npRQ) and oxidative rate of carbohydrates (CHO), and fat (FAT) in energy metabolism before and after radiofrequency ablation (RFA) therapy. Data are presented as mean ± standard deviation. ■, branched-chain amino acid (BCAA) ($n = 20$); □, Control ($n = 15$).

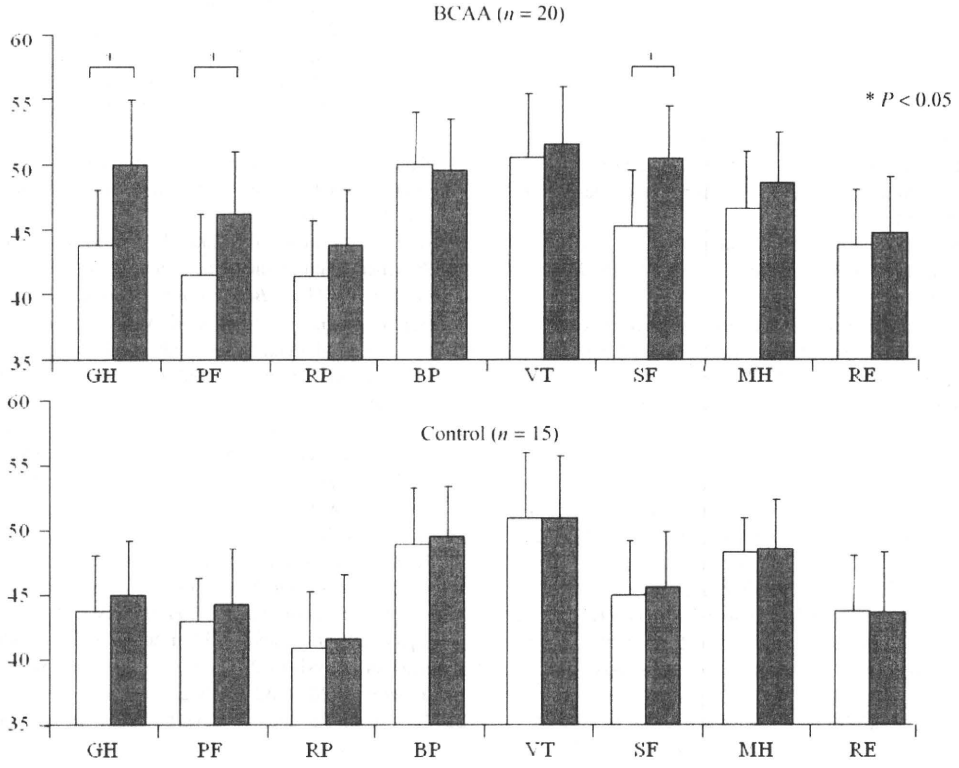

Figure 5 Changes in quality of life (QOL) with SF-8 score before and after radiofrequency ablation (RFA) in the two study groups. ■, After RFA (1 year); □, PreRFA. GH, general health perceptions; PF, physical functioning; RP, role physical; BP, bodily pain; VT, vitality; SF, social functioning; MH, mental health; RE, role emotional.

significantly between groups, but tended to be better in the BCAA group than in the control group. Okabayashi *et al.*[29] showed that perioperative supplementation with BCAA-enriched nutrients is beneficial for reducing morbidity associated with postoperative complications and in shortening the duration of hospitalization for patients with chronic liver disease undergoing liver resection. Moreover, Takeshita *et al.*[30] reported that the same therapy prevents suppression of liver function during a 2-week period after chemoembolization for HCC. Our data support these results.

On the other hand, a recent study has shown that the use of BCAA granules may prevent the occurrence of HCC in male LC patients showing overweight status and HCV infection.[18] The present study used BCAA-enriched nutrients, as the majority of subjects showed complicated malnutrition status. However, we could not confirm the prevention of HCC recurrence during the observation period. Several reasons must be considered: first, the observation period was short; second, compliance with BCAA-enriched nutrients was insufficient; and third, the number of subjects was small.

In conclusion, this first trial indicates that supplementation with BCAA-enriched nutrients can safely improve both PEM and QOL in HCC patients one year after RFA therapy. To clarify whether nutritional intervention with BCAA-enriched nutrients is effective for preventing HCC recurrence, a large-scale, long-term study is needed.

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Competing interests

The authors have no competing interests to declare.

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Short Communication

Changes in liver function parameters after percutaneous radiofrequency ablation therapy in patients with hepatocellular carcinoma

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Aim: To evaluate changes in liver function parameters and risk factors 1 year after percutaneous radiofrequency ablation (RFA) therapy in patients with hepatocellular carcinoma (HCC).

Methods: Subjects in this retrospective study comprised 45 patients with HCC who underwent RFA therapy (RFA alone, $n = 25$; transcatheter arterial embolization therapy before RFA, $n = 20$) and showed no recurrence of HCC 1 year after RFA. Serial changes in serum total bilirubin, albumin, prothrombin time and Child–Pugh score (CPs) were evaluated before and after RFA. In addition, Cox proportional hazards regression analysis was used to clarify risk factors for aggravation of liver function after RFA therapy.

Results: Serum albumin levels showed a significant decrease from before (3.6 ± 0.4 g/dL) to 12 months after RFA therapy (3.2 ± 0.4 g/dL; $P \leq 0.05$). CPs was significantly increased from before (6.4 ± 1.4) to both 6 months (6.8 ± 1.9; $P \leq 0.05$) and 12 months after RFA (6.9 ± 2.0; $P \leq 0.05$). Based on stepwise multivariate analysis, CPs of 9 or more before RFA was selected as a significant risk factor for long-term aggravation of liver function after RFA.

Conclusion: Liver function parameters, particularly serum albumin level, gradually and dominantly decreased in HCC patients with grade B and C according to the CPs classification over the course of 1 year after RFA therapy. A CPs of 9 or more represents a major risk factor for the aggravation of liver function after RFA therapy.

Key words: Child–Pugh score, hepatocellular carcinoma, liver cirrhosis, liver function parameters, percutaneous radiofrequency ablation therapy

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most significant malignancies among chronic liver diseases (CLD).[1] Surgical treatment such as hepatectomy is curative for HCC if the tumor is localized to the liver.[2] However, this therapy is frequently contraindicated by concomitant liver disease, particularly cirrhosis with severe liver damage. Furthermore, although liver transplantation remains the ultimate therapy for patients who fulfill the Milan criteria for liver transplantation and obtain a donor liver, this situation remains limited.[3]

Percutaneous radiofrequency ablation (RFA) therapy has recently been developed as an effective therapy for HCC patients who do not undergo surgery.[4,5] However, as hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causes of HCC in Japan, the recurrence rate of HCC after initial treatment is particularly high.[6,7] If patients with HBV- or HCV-related hepatitis cannot receive antiviral therapies and surgical treatment, repeated therapy for recurrence of HCC is required, resulting in deterioration of impaired liver function. Maintaining residual liver function capacity is thus very important to appropriately treat recurrent HCC. When HCC therapy is performed, changes to liver function are inevitable.[8] This phenomenon is not specific for RFA.

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However, precisely how residual liver function in HCC patients changes in the long term after RFA therapy remains unclear.

The goal is early detection and appropriate treatment of HCC in addition to stable maintenance of liver function to prolong the survival time of patients. The present study examined changes in liver function parameters according to Child–Pugh (CP) classification after RFA therapy and clarified risk factors for aggravation of liver function.

METHODS

Subjects

AMONG 55 PATIENTS with HCC who had undergone RFA therapy at the Division of Gastroenterology and Hepatology, Department of Internal Medicine, Iwate Medical University Hospital between January 2001 and March 2003, subjects comprised 45 patients who showed no HCC recurrence (local and/or intrahepatic) at 1 year after RFA therapy.

Patient profiles at the time of initial RFA therapy for HCC are shown in Table 1. During follow up, no patients received any other therapies, such as administration of albumin (Alb) infusion or antiviral treatments that might influence liver function. All patients with HCC showed CLD, comprising chronic hepatitis (CH) in eight patients and liver cirrhosis (LC) in 37 patients. CH and LC were diagnosed by biochemical examination of markers of liver fibrosis, imaging methods using endoscopy, ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI), and liver biopsy. Etiologies of hepatitis were: HBV, positive hepatitis B surface antigen; HCV, positive anti-hepatitis C antibody and/or HCV RNA; alcohol, more than 80 g/day ethanol consumption over 10 years; or unknown, no HBV, HCV or alcohol intake. Peripheral blood counts (red blood cells, white blood cells and platelet counts), liver function tests, prothrombin time (PT) and tumor markers in the blood (α-fetoprotein [AFP], lectin 3 fraction of AFP [AFP-L3] and protein induced by vitamin K absence or antagonist II [PIVKA-II]) were measured using commercial kits. Diagnosis of HCC and the number of nodules were detected by abdominal US, dynamic CT and/or MRI. Liver biopsy was performed in 12 patients to confirm the diagnosis of HCC.

Methods

The Cool-tip Radiofrequency System (Radionics, Burlington, MA, USA) has been used for RFA therapy of HCC in our institute since 2000. Indications for RFA were: (i) unresectable HCC or refusal of surgery; (ii) absence of uncontrollable ascites and hepatic encephalopathy; or (iii) absence of marked bleeding tendency. The general indications are patients with three lesions or less, all of which are 3 cm or less in diameter, or a single lesion of 5 cm or less. Twenty patients underwent transcatheter arterial embolization (TAE) prior to RFA therapy. For these patients, the mean interval from TAE to starting RFA therapy was 16.5 days (range, 8–58 days). RFA therapy was performed once or twice a week until complete necrosis of HCC was confirmed on dynamic CT.[9] RFA therapy was performed a mean of 1.8 ± 0.7 times in the study subjects.

Serum total bilirubin (T-Bil), Alb and PT were evaluated and CP score (CPs) was determined before and 3, 6

Table 1 Patients profiles at the time of initial treatment for hepatocellular carcinoma

Parameters	$n = 45$
Sex (male/female)	27/18
Age (years)	69 (66.2 ± 9.1)
Hepatitis B/C/NBNC/alcohol	3/37/3/2
Liver disease (CH/LC)	8/37
Child–Pugh grade (A/B/C)	19/16/2
Child–Pugh score (5/6/7/8/9/10 points)	11/8/9/3/4/2
Stage (I/II/III)	14/18/13
Number of tumor(s)	63
Solitary/multiple	24/21
Size of tumor (mm)	22 (25.2 ± 8)
Biological parameters	
T-Bil (mg/dL)	0.9 (0.9 ± 0.4)
Alb (g/dL)	3.6 (3.6 ± 0.4)
ALT (IU/L)	39 (41 ± 18)
Plt ($\times 10^4$/mm^3)	10.4 (11.2 ± 3.5)
PT (%)	76 (72 ± 14)
Tumor markers	
AFP (>100 ng/mL, positive/negative)	19/27
AFP-L3 (>10%, positive/negative)	10/35
PIVKA-II (>40 mAU/mL, positive/negative)	20/25
Treatment (with/without TAE)	20/25
BCAA administration (yes/no)	13/32
Liver volume (cm^3)	988.3 ± 245
Ablated volume (cm^3)	31.5 ± 25.4
Ablated rate (%)	3.2 ± 2.9

AFP, α-fetoprotein; AFP-L3, lectin 3 fraction of AFP; Alb, aluminum; ALT, alanine transaminase; BCAA, branched-chain amino acid; NBNC, non-B non-C; Plt, platelet counts; PIVKA-II, protein-induced vitamin K absence or antagonist II; PT, prothrombin time; TAE, transcatheter arterial embolization; T-Bil, total bilirubin.

and 12 months after RFA therapy.[10] Volumetric analysis of the entire liver and ablated portion was performed as follows: the area of liver parenchyma and ablated area were calculated using image-processing software attached to the CT system.[11,12] Parenchymal ablation rate was calculated as: ablated volume/liver parenchymal volume × 100 (%).[13] The relationship between change rate of CPs (ΔCPs) and grading of CP classification was evaluated. Aggravation of liver function was defined when CPs was increased by 2 or more at 12 months after RFA therapy. In addition, Cox proportional hazards regression analysis was performed to clarify risk factors for aggravation of liver function after RFA therapy.

Statistics

Laboratory data are shown as mean ± standard deviation. Statistical analyses were performed using StatView ver. 5.0 software. Cox proportional hazards regression was performed to evaluate risk factors for aggravation of liver function using demographic data obtained prior to initial RFA. Univariate analysis evaluated 20 factors: age; sex; HCV; T-Bil; alanine aminotransferase; Alb; platelet count (Plt); PT; AFP; AFP-L3; PIVKA-II; grading of CP classification; CPs; tumor size; number of tumor nodules; combination therapy with TAE; branched chain amino acids (BCAA) treatment; ablated rate; recurrence of HCC; and complications. Parameters identified as significant in univariate analysis were tested in the multivariate Cox proportional hazards model for all patients.

RESULTS

Serial changes in CPs after RFA therapy

SERUM ALB LEVELS decreased significantly after RFA therapy from 3.6 ± 0.4 g/dL before RFA to 3.5 ± 0.3 g/dL after 6 months and 3.2 ± 0.4 g/dL after 12 months ($P \leq 0.05$). Serum T-Bil and PT levels were unchanged after RFA (T-Bil: before, 0.9 ± 0.4 mg/dL; after 12 months, 1.0 ± 0.4 mg/dL; PT: before, 76.1 ± 14.5%; after 12 months, 74.8 ± 15.2%). CPs was significantly increased after RFA from 6.4 ± 1.4 before RFA to 6.8 ± 1.9 after 6 months ($P \leq 0.05$) and 6.9 ± 2.0 after 12 months ($P \leq 0.01$). Serial changes in ΔCPs according to grading of CP are shown in Figure 1. No change in ΔCPs was seen in CH or LC patients with grade A at 12 months after RFA therapy, while significant increases were noted in grade B and C LC patients. Changes in Alb, T-Bil, and CPs did not differ between patients receiving RFA alone and those receiving TAE ± RFA (data not shown).

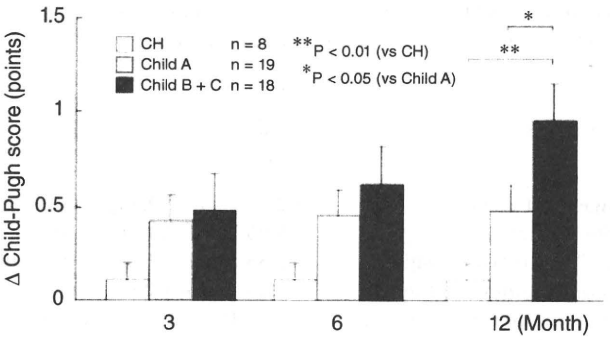

Figure 1 The changes of Δ Child–Pugh score after radiofrequency ablation.

Risk factors for aggravation of liver function

Univariate analysis showed CPs (≥9), Plt and Alb as predictive factors for deterioration of liver function after RFA therapy, while CPs (≥9) was the only significant risk factor identified by stepwise multivariate analysis (Table 2). In addition, no significant differences were observed between patients with and without TAE.

DISCUSSION

THE PRESENT STUDY evaluated serial changes in T-Bil, Alb and PT, three parameters used in the CP classification, over the course of 12 months following RFA therapy. We also tried to identify risk factors for long-term aggravation of liver function after RFA. Our data indicated that: (i) Alb is significantly decreased 12 months after RFA; (ii) CPs is significantly increased both 6 and 12 months after RFA; and (iii) CPs in patients with CH and grade A LC does not change after RFA. Furthermore, multivariate analysis identified CPs of 9 or more as a major risk factor for the aggravation of liver function following RFA. Taken together, these data suggest that appropriate nutritional support is necessary for HCC patients over grade B and C or with a CPs of 9 or more when RFA therapy is performed.

However, the study population comprised patients receiving two therapies, namely, patients treated with RFA therapy alone and patients treated with TAE prior to RFA therapy. We therefore did not confirm a direct influence of RFA therapy alone, although liver function tests before RFA therapy showed similar findings in both groups and the performance of TAE was not identified as a significant risk factor for the aggravation of liver func-

Table 2 Risk factors contributing to degradation of functional reserve of the liver after radiofrequency ablation

Univariate analysis		
Variables	Odds ratio (95% CI)	*P*
Age (>69 years)	2.18 (0.45–10.53)	0.329
Sex (male)	5.95 (0.61–53.3)	0.111
HCV antibody (positive)	0.58 (0.94–3.59)	0.559
Size of tumor (>22 mm)	0.45 (0.95–2.22)	0.329
Number of tumor (multiple)	1.44 (0.25–8.23)	0.682
Child classification (Child B/C vs Child A/CH)	3.07 (0.79–14.87)	0.163
Child–Pugh score (≥9 points)	16.5 (2.39–127.53)	0.004
T-Bil. (>0.9 mg/dL)	1.57 (0.32–7.59)	0.124
Alb (<3.5 g/dL)	5.18 (1.02–26.43)	0.047
ALT (>80 IU/l)	1.92 (0.72–3.53)	0.694
Plt ($<9.4 \times 10^4/mm^3$)	7.91 (1.23–40.75)	0.028
PT (<70%)	3.16 (0.52–17.53)	0.194
AFP (>100 ng/mL)	0.87 (0.19–4.52)	0.873
AFP-L3 (>10%)	1.55 (0.19–8.53)	0.685
PIVKA-II (>40 mAU/mL)	0.81 (0.18–3.23)	0.835
Treatment (with/without TAE)	0.76 (1.47–3.39)	0.668
BCAA administration (yes)	2.78 (0.88–13.53)	0.148
Ablated rate (>3.5%)	2.35 (0.15–12.53)	0.651
Recurrence (+ vs –)	3.10 (0.57–16.58)	0.168
Complication (+ vs –)	2.54 (0.19–31.55)	0.483
Stepwise multivariate analysis		
Variables	Odds ratio (95% CI)	*P*
Child–Pugh score (≥9 points)	8.02 (1.05–5.67)	0.024
Plt ($<9.8 \times 10^4/mm^3$)	3.52 (0.59–1.24)	0.347
Alb (<3.5 g/dL)	2.52 (0.94–1.14)	0.401

Alb, aluminum; AFP, α-fetoprotein; AFP-L3, lectin 3 fraction of AFP; ALT, alanine aminotransferase; BCAA, branched-chain amino acid; CI, confidence interval; HCV, hepatitis C virus; PIVKA-II, protein-induced vitamin K absence or antagonist II; Plt, platelet counts; PT, prothrombin time; TAE, transcatheter arterial embolization; T-Bil, total bilirubin.

tion after RFA therapy. Because no studies have yet compared changes in liver function tests between RFA therapy and TAE therapy, the differences between these therapies need to be clarified in the future.

Patients with advanced LC and malnutrition are well known to exhibit poor prognosis.[14] Previous studies have shown that p.o. administration of BCAA can improve nutritional status and event-free survival in cirrhosis.[15] Recent studies have also suggested potential benefits of BCAA administration in cirrhotic patients with HCC.[16–19] The present study, however, could not convincingly examine the effects of BCAA in HCC patients receiving RFA, because the number of patients receiving BCAA was small (13 of 45 patients, grade A, $n = 4$; grade B or C, $n = 9$) and doses and formulations of BCAA varied among patients. Further studies are necessary to fully evaluate the effects of BCAA on nutritional status and recurrence of HCC in patients with LC following RFA.

In addition, as shown in the results, BCAA treatment was not a significant risk factor for deterioration of liver function after RFA therapy in univariate analysis. The following reasons are considered to explain why BCAA treatment in this study did not improve serum Alb level. First, the number of patients receiving BCAA treatment was very small. Second, administered doses and formulations of BCAA (e.g. BCAA granules and BCAA-enriched nutrients) were not fixed. In the future, differences between BCAA granules and BCAA-enriched nutrients should be evaluated with regard to influences on nutritional status and recurrence of HCC in LC patients. The present results might be useful as baseline data to estimate the effects of nutritional support therapies among HCC patients receiving RFA therapy.

In conclusion, serum Alb level gradually decreases over the course of 1 year after RFA therapy in LC patients with grade B or C according to the CP classification. A CPs of 9 represents a critical baseline to estimate progression to liver failure in HCC patients after receiving RFA therapy.

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BRIEF ARTICLE

Transcatheter arterial chemoembolization with a fine-powder formulation of cisplatin for hepatocellular carcinoma

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Abstract

AIM: To evaluate the efficacy of transcatheter arterial chemoembolization (TACE) using a suspension of a fine-powder formulation of cisplatin (DDPH) for hepatocellular carcinoma (HCC).

METHODS: The study population was comprised of 164 patients who were treated by TACE alone. Of these patients, 76 underwent TACE using a suspension of DDPH in lipiodol (LPD) (DDPH group), and the remaining 88 underwent TACE with an emulsion of doxorubicin (ADM) with LPD (ADM group). We compared the DDPH group with the ADM group in terms of the objective early response rate, progression free survival (PFS) and overall survival (OS).

RESULTS: The objective early response rate in the DDPH group was significantly higher than that in the ADM group (54% *vs* 24%, $P < 0.001$). The PFS rate in the DDPH group was also significantly higher than that in the ADM group ($P < 0.001$). Moreover, the OS in the DDPH group was significantly longer than that in the ADM group ($P = 0.002$). Although the incidence rate of nausea or vomiting in the DDPH group was higher than that in the ADM group, the ADM group showed a higher incidence rate of the adverse events of hepatic arterial damage and leucopenia. No other serious complications were observed in either group.

CONCLUSION: We conclude that TACE using a suspension of DDPH in LPD could be a useful treatment for HCC.

Key words: Hepatocellular carcinoma; DDPH; Transcatheter arterial chemoembolization; Cisplatin; Doxorubicin

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the cancer with the sixth highest incidence in the world[1]. The number of deaths from HCC is also increasing throughout the world[2-5]. Development of new treatments for HCC has

helped improve the patient prognosis[6,7]. Local ablating therapies such as percutaneous ethanol injection (PEI) or radiofrequency ablation (RFA) have been effective in cases of limited tumor spread and are increasingly used[7,8]. However, the majority of patients are not eligible for these modalities because of large tumor size or diffuse tumor growth. In these patients regional transcatheter arterial chemoembolization (TACE) has been widely used as a palliative treatment[9,10]. Two randomized trials from Europe and Asia recently confirmed a survival benefit after TACE using gelfoam and iodized oil (lipiodol) compared to conservative treatment[11,12]. In recent years, TACE using an emulsion of doxorubicin (ADM) with lipiodol (LPD) (ADM-LPD emulsion) followed by embolization with a gelatin sponge has been employed commonly for HCC treatment[13,14]. However, the tumors have been demonstrated to show a high frequency of recurrence after TACE[10,15,16]. Cisplatin (CDDP), a platinum compound, is an effective anticancer agent used in the treatment of various malignancies[17]. Researchers have recently reported that TACE using a suspension of CDDP powder in LPD may be more effective against unresectable HCC as compared with TACE using ADM-LPD emulsion[18,19]. However, only limited institutions have used this for TACE because it is laborious to refine the CDDP powder. Since 2004, a fine-powder formulation of CDDP (DDPH, IA-call; Nippon Kayaku, Tokyo, Japan) has also been available as a therapeutic agent for intra-arterial infusion in Japan. As a result, TACE using DDPH has become widespread in Japanese institutions. Nevertheless, the efficacy of TACE using DDPH-LPD suspension has not yet been reported.

In this article, we compared the effectiveness with regard to the response rate (RR), progression free survival (PFS) and overall survival (OS) between TACE using a suspension of DDPH in LPD (DDPH-LPD suspension) and ADM-LPD emulsion. Moreover, we analyzed the prognostic factors for clinical outcome of patients treated with TACE.

MATERIALS AND METHODS

Patients

Between January 2006 and July 2009, 164 HCC patients who showed no indication for surgical resection or local ablation therapy such as RFA and PEI therapy were enrolled in the study. HCC was diagnosed by the distinctive findings on ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and angiography, and the serum levels of des-γ-carboxy prothrombin (DCP) and α-fetoprotein (AFP). Histologic examination was not always carried out. Liver function was evaluated according to the Child-Pugh classification[20]. Tumor stage was judged by the TNM classification established by the International Union Against Cancer[21]. The extent of portal vein invasion was classified as follows: Vp 0, no invasion of the portal vein; Vp 1, invasion of the third or more distal branch of the left or right portal vein; Vp 2, invasion of the second branch of the portal vein; Vp3, invasion of the first branch of the portal vein; and Vp4, invasion of the trunk of the portal vein. After being presented with the clinical results of previous studies of TACE using DDPH-LPD suspension or TACE using ADM-LPD emulsion, all 164 patients themselves selected the therapeutic option on the basis of informed consent. All of the enrolled patients met the eligibility criteria for inclusion in the analysis described in the next paragraph. The patients were divided into two groups: one group consisting of 76 patients who underwent TACE using DDPH-LPD suspension (DDPH group), and another group consisting of 88 patients who underwent TACE using ADM-LPD emulsion (ADM group). They were all treated by TACE alone.

Informed consent was obtained from all of the patients. The study protocol was approved by the Ethics Committee of Iwate Medical University and the study was conducted in accordance with the Declaration of Helsinki 1975.

Eligibility criteria

The eligibility criteria of the patients for this study were as follows: (1) No indication for surgical resection or local ablation therapy such as RFA and PEI therapy; (2) No evidence of extra-hepatic metastasis; (3) No tumor thrombus in the main trunk of portal vein; (4) No evidence of active heart or renal diseases meeting the contraindications for ADM and CDDP therapy, respectively; (5) Eastern Cooperative Oncology Group (ECOG) performance status (PS)[22] level 0-2; (6) Hypervascular tumors showing enhancement during angiography; (7) Bidimensionally measurable hepatic lesions; (8) No uncontrolled ascites or pleural effusion; and (9) Total serum bilirubin (T-Bil) less than 3 mg/dL.

The presence of underlying liver diseases such as hepatitis or cirrhosis was confirmed by laboratory, radiological examinations and pathological examinations. We classified the chronic hepatitis patients into Child-Pugh class A, because chronic hepatitis is a known precirrhotic condition.

Preparation of the agents for TACE

We used DDPH or ADM (Adriacin; Kyowa Hakko Kogyo, Tokyo, Japan) mixed with LPD (iodized oil; Andre Guerget, Aulnay-sous-Bois, France).

The DDPH-LPD suspension was prepared by mixing 50 mg of DDPH into 3-10 mL of LPD.

The ADM-LPD emulsion was prepared by the following procedure: 10-30 mg of ADM was dissolved in 1-2 mL of a contrast medium (Iomeron; Eisai Co., Ltd., Tokyo, Japan) and then mixed with 3-10 mL LPD.

The dosage of LPD and the anticancer drugs was adjusted depending on the tumor size, number of tumors, degree of liver impairment and renal function, however, the maximum dose of LPD was not allowed to exceed 10 mL.

Treatments

Hepatic arteriography, superior mesenteric arterial porto-

venography, CT during arteriography and CT during arterio-portography were performed to define the size and locations of tumor nodules and to exclude tumor thrombus in the main trunk of the portal vein. Following hepatic angiography, a catheter was selectively inserted into the hepatic artery supplying the target tumor and the DDPH-LPD suspension or the ADM-LPD emulsion was injected. In patients with several tumors in the liver, superselective catheterization was performed for each lesion. If superselective catheterization was not possible, the DDPH-LPD suspension or the ADM-LPD emulsion was injected into the right and left main hepatic artery distal to the origin of the cystic artery. After the injection, arterioembolization was performed used gelatin sponge particles (Gelpart; Nippon Kayaku, Tokyo, Japan) mixed with contrast medium.

All the patients were followed up with US, CT and/or MRI after 1 mo and every 3 mo thereafter. TACE was undertaken again when relapse of the treated lesions and/or new hepatic lesions were detected. These patients received additional TACE using the same agent during the follow-up period. The TACE was repeated until complete regression of the tumor was obtained, or until the patient could no longer be treated.

Post treatment assessment

Early tumor response was assessed by US, CT and/or MRI, conducted 1 mo after the initial treatment. We regarded LPD accumulation in the tumor as representing a necrotic area, based on previous reports of such LPD retention areas corresponding to the necrotic areas on CT[23-26]. By measurement of the two largest perpendicular diameters of the tumor, we classified the tumor response into four categories using the following criteria: complete response (CR), complete disappearance or 100% necrosis of all tumors; partial response (PR), reduction and/or necrosis, with at least 50% decrease of all the measurable lesions; progressive disease (PD), an increase of the tumor size exceeding 25% of all the measurable lesions or appearance of a new lesion; stable disease (SD), disease not qualifying for classification as CR, PR, PD.

Toxicity was evaluated by the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0).

Statistical analysis

The differences in the background clinical characteristics of the patients between the DDPH group and ADM group were assessed by Mann-Whitney's *U* test, logistic regression test, or the χ^2 test, as appropriate.

PFS and OS were calculated from the date of start of the therapy to the date on which tumor progression was documented and the date of death of the patient, respectively. Both were assessed by the Kaplan-Meier life-table method, and the differences between the two treatment groups were evaluated by the log rank test. Univariate analysis to identify the predictors of survival in the patients was conducted by the Kaplan-Meier life-table method, and the differences between the two groups were evaluated by the log rank test. Multivariate analysis to identify the predictors of survival was conducted using the Cox proportional hazards model. Statistical significance was defined as a *P* value of less than 0.05. All of the above analyses were performed using the SPSS software (version 11, SPSS, Chicago, IL, USA).

Table 1 Patient characteristics

Characteristics	DDPH group	ADM group	*P* value
No. of patients	76	88	
Age (yr) [median, (range)]	67 (32-87)	69 (21-90)	0.093
Gender (male/female)	57/19	52/36	0.031
Etiology (HBV/HCV/NBNC)	11/50/15	8/64/16	0.508
Child-Pugh classification (A/B/C)	47/26/3	45/36/7	0.303
TNM classification (I - II / III-IV)	10/66	24/64	0.026
Tumor size (≤ 3.0/> 3.0 cm)	21/55	30/58	0.373
Number of tumors (1-3/≥ 4)	35/41	46/42	0.427
PVTT (Vp0-2 / Vp3)	62/14	80/8	0.080
Total bilirubin (≤ 1.5/> 1.5 mg/dL)	66/10	75/13	0.906
Albumin (≤ 3.5/> 3.5 g/dL)	38/38	45/42	0.822
AFP (≤ 1000/> 1000 ng/mL)	68/8	79/8	0.776
DCP (≤ 1000/> 1000 mAU/mL)	59/14	73/14	0.609

Data are expressed as median with range values, or the number of patients. The stages of HCC by TNM classification are clustered into two groups (I - II and III-IV). The tumor characteristics and other parameters are classified as follows: tumor size: ≤ 3.0, > 3.0 cm; tumor number: 1-3, > 4; extent of PVTT: Vp 0-2, and Vp 3; serum bilirubin: ≤ 1.5, > 1.5 mg/dL; serum albumin: ≤ 3.5, > 3.5 g/dL; serum AFP levels: ≤ 1000, > 1000 ng/mL. Serum DCP levels: ≤ 1000, > 1000 mAU/mL. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: Negative for hepatitis B surface antigen and HCV antibody; PVTT: Portal vein tumor thrombosis; AFP: α-fetoprotein; DCP: Des-γ-carboxy prothrombin; DDPH group: Using a suspension of DDPH in lipiodol (LPD); ADM group: With an emulsion of doxorubicin (ADM) with LPD.

RESULTS

Patient profile

The characteristics of the 164 patients of both groups are summarized in Table 1. There were 109 male and 55 female patients, ranging in age from 21 to 90 years old (mean, 68 years old).

Regarding the assessment of differences in the characteristics of the patients, there were significant differences in the gender distribution and in the TNM classification between the two groups, i.e. there was a higher proportion of males ($P = 0.031$) and more subjects with advanced TNM classification ($P = 0.026$) in the DPHH group. There were no significant differences in any of the other characteristics between the two groups.

Treatments and early tumor response

The median follow-up period was 13.1 mo (range: 1-40 mo). We performed 392 TACE procedures (157 sessions in the DDPH group, 235 sessions in the ADM group) in 164 patients. The median number of TACE

Table 2 Early tumor response *n* (%)

	DDPH (n = 76)	ADM (n = 88)	P value
CR	2 (3)	5 (6)	
PR	39 (51)	16 (18)	
SD	23 (30)	5 (6)	
PD	12 (16)	62 (70)	
CR + PR	41 (54)	21 (24)	< 0.001

Data are expressed as number of patients and percentages. DDPH group: Using a suspension of DDPH in lipiodol (LPD); ADM group: With an emulsion of doxorubicin (ADM) with LPD; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

Table 3 Univariate analysis for identifying the predictors of survival

Variable	Hazard ratio	95% CI	P value
Treatment regimen (ADM *vs* DDPH)	0.580	0.325-1.035	0.065
Age (≤ 65 yr *vs* > 65 yr)	1.286	0.741-2.231	0.372
Gender (female *vs* male)	1.651	0.944-2.888	0.079
Etiology (NBNC *vs* HBV/HCV)	0.734	0.432-1.246	0.252
Child Pugh classification (A *vs* B/C)	1.142	0.689-1.891	0.607
TNM classification (Ⅰ-Ⅱ *vs* Ⅲ-Ⅳ)	2.765	1.252-6.106	0.012
Tumor size (≤ 3.0 cm *vs* > 3.0 cm)	2.094	1.161-3.776	0.014
Number of tumors (1-3 *vs* ≥ 4)	2.612	1.535-4.444	0.001
PVTT (Vp0-2 *vs* Vp3)	4.714	2.520-8.819	< 0.001
Total bilirubin (≤ 1.5 mg/dL *vs* > 1.5 mg/dL)	1.730	0.874-3.422	0.116
Albumin (≤ 3.5 g/dL *vs* > 3.5 g/dL)	0.996	0.603-1.647	0.989
AFP (≤ 1000 ng/mL *vs* > 1000 ng/mL)	1.323	0.528-3.315	0.551
DCP (≤ 1000 mAU/mL *vs* > 1000 mAU/mL)	2.396	1.288-4.459	0.005

DDPH group: Using a suspension of DDPH in lipiodol (LPD); ADM group: With an emulsion of doxorubicin (ADM) with LPD; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: Negative for hepatitis B surface antigen and HCV antibody; PVTT: Portal vein tumor thrombosis; AFP: α-fetoprotein; DCP: Des-γ-carboxy prothrombin.

procedures was 2 sessions (range: 1-5 sessions) in the DDPH group and 3 sessions (range: 1-6 sessions) in the ADM group. The median interval to the re-treatment with TACE was 9.4 mo in the DDPH group and 3.8 mo in the ADM group. One hundred and ten sessions (70.1%) in the DDPH group and 170 sessions (72.3%) in the ADM group were treated by superselectivity of TACE. There was no significant difference in the incidence of superselectivity of TACE between the two groups.

In the DDPH group, 2 (3%), 39 (51%), 23 (30%) and 12 (16%) patients showed CR, PR, SD and PD, respectively. In the ADM group, 5 (6%), 16 (18%), 5 (6%) and 62 (70%) patients showed CR, PR, SD and PD, respectively. Therefore, the objective early response rate of the DDPH group (54%) was significantly higher than that in the ADM group (24%). The difference in the rate between the two groups was statistically significant (P < 0.001) (Table 2).

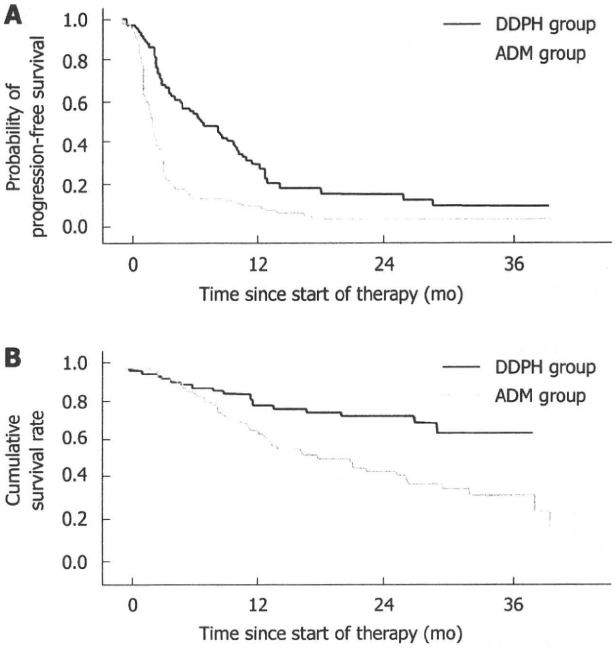

Figure 1 Comparison of the progression-free survival rates (A) and overall survival (B) between the DDPH and ADM groups. A: The progression-free survival rate was significantly higher in the DDPH group than in the ADM group (log-rank test: P < 0.001); B: The overall survival was significantly longer in the DDPH group than in the ADM group (log-rank test: P = 0.002). DDPH group: Using a suspension of DDPH in lipiodol (LPD); ADM group: With an emulsion of doxorubicin (ADM) with LPD.

PFS

The median PFS was 8.6 mo in the DDPH group and 3.0 mo in the ADM group. The PFS rates at 6, 12, 24 and 36 mo were 58%, 32%, 18% and 11%, respectively, in the DDPH group. In contrast, the corresponding values were 18%, 10%, 5% and 5%, respectively, in the ADM group. The PFS rates in the DDPH group were significantly higher than those in the ADM group (P < 0.001) (Figure 1A).

Survival

The median survival time (MST) in the DDPH and ADM groups was "not reached" and 20.8 mo, respectively. The OS values at 6, 12, 24, and 36 mo were 92%, 81%, 76% and 67%, respectively, in the DDPH group. The corresponding values in the ADM group were 87%, 68%, 46% and 37%, respectively. The OS in the DDPH group was significantly longer than that in the ADM group (P = 0.002) (Figure 1B).

Univariate analysis to identify the predictors of survival indicated five possible factors affecting the survival: TNM classification; tumor size; number of tumors; portal vein tumor thrombosis (PVTT) and serum DCP level. The treatment regimen was close to being statistically significant (P = 0.065) for survival (Table 3). Multivariate analysis performed using factors that were considered

Table 4 Multivariate analysis for identifying predictors of survival

Variable	Hazard ratio	95% CI	*P* value
Treatment regimen (ADM *vs* DDPH)	0.329	0.149-0.726	0.006
Gender (female *vs* male)	2.291	1.174-4.470	0.015
Number of tumors (1-3 *vs* ≥ 4)	6.541	3.201-13.363	< 0.001
PVTT (Vp0-2 *vs* Vp3)	6.704	2.581-17.418	< 0.001
Albumin (≤ 3.5 g/dL *vs* > 3.5 g/dL)	0.311	0.157-0.612	0.001

DDPH group: Using a suspension of DDPH in lipiodol (LPD); ADM group: With an emulsion of doxorubicin (ADM) with LPD; PVTT: Portal vein tumor thrombosis.

significant ($P < 0.1$) on univariate analysis identified the treatment regimen, gender, number of tumors, PVTT, and serum albumin as independent factors affecting the survival (Table 4).

Adverse effects

Table 5 shows a summary of the adverse effects in the two groups. The incidence rate of nausea/vomiting in the DDPH group was significantly higher than that in the ADM group ($P < 0.001$). In addition, the incidence rates of hepatic arterial damage (HAD) after TACE and leucopenia in the ADM group were significantly higher than those in the DDPH group ($P < 0.001$ and $P = 0.002$, respectively). We observed HAD in 17 patients. Although one patient in the DDPH group was observed to have slight wall irregularity of the hepatic artery (HA), HAD associated with TACE did not interfere with catheterization at the next TACE session. On the other hand, in the ADM group, we observed slight wall irregularity of HA in six patients, overt stenosis of HA in four patients and occlusion of HA in six patients. In six patients who were observed as having occlusion of HA, it became impossible to treat with repeated TACE.

No other serious complications or treatment-related deaths were observed in either group.

Table 5 Adverse events *n* (%)

Adverse effect	Treatment group (%)		*P* value
	DDPH group (*n* = 76)	ADM group (*n* = 88)	
Nausea/vomiting	64 (84)	48 (55)	< 0.001
Fever	61 (80)	73 (83)	0.571
Abdominal pain	53 (69)	63 (72)	0.958
Elevation of transaminase levels	55 (72)	62 (71)	0.993
Liver abscess	1 (1)	2 (2)	0.765
Hepatic arterial damage	1 (1)	16 (18)	< 0.001
Renal or liver failure	0 (0)	2 (2)	0.229
Leucopenia	3 (4)	12 (14)	0.002
Thrombocytopenia	4 (5)	6 (7)	0.650
Fatigue	21(28)	27 (31)	0.839

DDPH group: Using a suspension of DDPH in lipiodol (LPD); ADM group: With an emulsion of doxorubicin (ADM) with LPD; Data are expressed as number of patients, with the percentages indicated in parentheses.

DISCUSSION

TACE has been widely used for the treatment of unresectable HCC[9,10]. The most commonly used agent used in TACE for HCC treatment is ADM-LPD emulsion, followed by embolization with a gelatin sponge[13,14]; however, the tumors frequently recur[10,15,16] or residual tumors are observed at a high incidence. CDDP is an effective anticancer agent used in the treatment of various malignancies[17]. It has been reported to exert its actions by binding to the DNA in cancer cells, inhibiting DNA synthesis and subsequent cellular division. The antitumor activity of CDDP is closely associated with the serum concentration of the drug[27]. Therefore, the antitumor activity can be enhanced by increase of the dose. LPD acts as a selective carrier of anticancer agents and as an embolic material[23]; the anticancer agent is gradually released from the iodized oil. Although the mechanism of topical accumulation of LPD in the tumor is not yet precisely understood, it is used nonetheless to achieve a targeting drug delivery system with long-lasting accumulation in the tumor and gradual drug release. Consequently, augmented antitumor efficacy and milder side-effects have come to be expected with the use of this substance for TACE. In fact, Morimoto *et al*[28] investigated the pharmacological advantages of TACE using DDPH for hypervascular hepatic tumors in animal experiments. They reported that the tumor concentration of the platinum agent in the DDPH-LPD-TACE group was about 14 times higher than that in the DDPH-hepatic arterial infusion (HAI) group. In addition, they reported that the plasma concentrations of the platinum agent at 5 and 10 min from start of the infusion were lower in the DDPH-LPD-TACE group than those in the DDPH-HAI group. Recently, Ono *et al*[18] reported that TACE using a suspension of CDDP powder in LPD was more effective than that using ADM-LPD emulsion against unresectable HCC. Other investigators have also frequently reported favorable results obtained with TACE using a suspension of CDDP powder in LPD in HCC patients[19,29]. However, the CDDP powder for this therapy is difficult to produce because of the characteristics of the drug formulation. Therefore, CDDP powder had to be a custom-made formulation in individual institutions[30]. Consequently, when an institution was able to dispense CDDP powder in its own pharmacy department, TACE using a suspension of CDDP powder in LPD was undertaken.

A fine-powder formulation of CDDP, namely "DDPH", for intra-arterial infusion has been available for HCC treatment since 2004 in Japan. Dispensing of CDDP powder improved with the development of DDPH, and DDPH has now come to replace CDDP powder. Using DDPH-LPD suspension for TACE in HCC patients was expected to yield better therapeutic outcomes; therefore, TACE using DDPH became widespread in Japanese institutions. Nevertheless, the efficacy of TACE using DDPH-

LPD suspension has not yet been reported. Therefore, we compared the outcomes of TACE using DDPH-LPD suspension and ADM-LPD emulsion.

Analysis of the results in our study revealed that the objective response rate in the DDPH group was significantly higher than that in the ADM group. Moreover, the OS of the patients in the DDPH group was significantly longer than that of the patients in the ADM group. This could be explained as being due to the fact that TACE with ADM cannot be repeated as required because of the high frequency of adverse effects of ADM such as leucopenia, severe vascular changes and occlusion of the hepatic artery[18,31,32]. In fact, the incidences of leucopenia and HAD in the ADM group in our study were significantly higher than those in the DDPH group. Considering the fact that TACE is often repeated in most patients, longer patency of the hepatic artery is preferable for properly deploying the lipiodol mixture and embolic agents into the tumor. In addition, we conclude that anthracyclines such as ADM may be relatively less effective against HCC; this is because of the high expression level of P-glycoprotein, which transports antitumor agents such as anthracyclines or vinca alkaloids from cells with a high active efflux mechanism, in HCC tumors[33].

On the other hand, Pelletier *et al*[34] reported that TACE with CDDP sometimes caused severe complications, such as acute hepatic failure. The treatment also did not produce any significant improvement of the survival rate in this study. Severe complications could be expected with the high doses (2 mg/kg) of CDDP used in their study. Therefore, we performed TACE using DDPH-LPD suspension in our study with half of the dose (50 mg = 1 mg/kg) that they had used. Modification of the CDDP dose used for the treatment to DDPH 50 mg in our study resulted in a lower severity of complications.

Takayasu *et al*[35] reported a nationwide prospective cohort study which was performed in 8510 patients with unresectable HCC who underwent TACE using an emulsion of lipiodol and anticancer agents followed by gelatin sponge particles as an initial treatment. In their report, multivariate analysis for the factors affecting survival showed significant differences in degree of liver damage, AFP, maximum tumor size, number of lesions, and PVTT. In contrast to their report, we could not observe AFP value as a prognostic factor in our multivariate analysis. This may be due to fewer in the study population and a shorter observation period in our study compared with their study. In addition, a cut-off value for AFP of 1000 ng/mL in our study was much higher than that (400 ng/mL) in their study because we aimed to analyze the difference in the effect of TACE with the extent that HCC had progressed. Therefore, we could not observe AFP value as a prognostic factor in our multivariate analysis.

This study was not a well-controlled prospective study. Nevertheless, the patients in the two groups had fairly similar characteristics with regard to age, etiology, Child-Pugh classification, tumor size, number of tumors, PVTT, total bilirubin, albumin, AFP, and DCP. In relation to the differences in the characteristics of the patients, the DDPH group had a significantly higher proportion of males and a more advanced stage in TNM classification than the ADM group. Several investigators[36,37] have shown that TNM classification and tumor stage are independent prognostic factors for survival of patients who are treated by TACE. Therefore, we forecast that the prognosis of the CDDP group was worse than that of the ADM group, because the DDPH group had more advanced stage in TNM classification than the ADM group. However, the OS in the DDPH group was significantly longer than that in the ADM group. Moreover, to avoid the confounding effects of any deviations in the patient characteristics causing an impact on the results, we used the multivariate analysis for comparison of the efficacy between the regimens. The analysis identified the treatment regimen employed for the TACE as one of the most important prognostic factors. Compared to a previous report[18] describing TACE using a suspension of CDDP powder in LPD, the objective response rate and OS in the DDPH group in our study were significantly higher.

Considering these facts, we conclude that TACE using DDPH-LPD suspension could be a useful treatment strategy for HCC patients. To confirm these results, randomized controlled trials comparing TACE using DDPH-LPD suspension with TACE using ADM-LPD suspension for patients with HCC are mandatory.

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COMMENTS

Background

In recent years, transcatheter arterial chemoembolization (TACE) using an emulsion of doxorubicin (ADM) with lipiodol (LPD) (ADM-LPD emulsion) followed by embolization with a gelatin sponge has been employed commonly for hepatocellular carcinoma (HCC) treatment. However, the tumors have been demonstrated to show a high frequency of recurrence after TACE.

Research frontiers

Cisplatin, a platinum compound, is an effective anticancer agent used in the treatment of various malignancies. Since 2004, a fine-powder formulation of cisplatin (DDPH, IA-call; Nippon Kayaku, Tokyo, Japan) has also been available as a therapeutic agent for intra-arterial infusion in Japan. Researchers have recently reported that TACE using a suspension of cisplatin powder in LPD may be more effective against unresectable HCC as compared with TACE using ADM-LPD emulsion. Therefore, TACE using DDPH has become widespread in Japanese institutions. However, the efficacy of TACE using DDPH-LPD suspension has not yet been reported.

Innovations and breakthroughs

In this article, the authors reported the effectiveness of TACE using DDPH-LPD suspension compared with that using ADM-LPD emulsion.

Applications

Although randomized controlled trials comparing TACE using DDPH-LPD suspension with TACE using ADM-LPD suspension for patients with HCC are needed, this study shows that TACE using DDPH-LPD suspension can be a useful treatment strategy for HCC patients.

Terminology

TACE: Transarterial chemoembolization, a procedure in which the blood supply to a tumor is blocked (embolized) and chemotherapy is administered directly into the tumor.

Peer review

Kasai *et al* evaluated the efficacy of TACE using a suspension of DDPH for HCC. The authors indicated that early response rate, progression free survival and overall survival in the DDPH group was significantly higher than that in the ADM group.

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今月のテーマ●肝硬変の包括的マネージメント

肝性脳症治療の up-date

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要旨：肝硬変に起因する肝性脳症の病態には肝細胞障害と門脈大循環短絡の２つの要因が相互に関連している．肝性脳症は精神神経障害の程度により昏睡Ⅰ度からⅤ度までに分類されるが，最近，明らかな精神神経症状がなく定量的精神神経機能検査ではじめて異常を指摘される潜在性（ミニマム）肝性脳症の病態が注目されている．しかし，その診断法についてのコンセンサスはいまだ得られていない．治療では血液アンモニア濃度のコントロール，アミノ酸代謝異常の是正を目標に合成二糖類，難吸収性抗菌薬，特殊組成アミノ酸製剤（分岐鎖アミノ酸製剤）などが用いられているが，その効果は肝の重症度に大きく影響される．肝不全が高度の例に対しては血液浄化療法，肝移植も行われている．蛋白・エネルギー代謝異常の是正が肝性脳症の顕性化予防，長期予後の改善には重要な対策と考えられる．

索引用語：肝硬変，肝性脳症，合成二糖類，難吸収性抗菌薬，分岐鎖アミノ酸療法

はじめに

肝性脳症（肝性昏睡）は肝硬変（肝癌合併例も含む）の経過中にみられる重篤な合併症の１つである．肝性脳症の発生機序には，アンモニアを中心とした中毒性物質による多因子説，アミノ酸代謝異常説，偽性神経伝達物質説，γアミノ酪酸(GABA)/ベンゾジアゼピン受容体複合体異常説などがあるが，単一の機序では説明が困難である．近年，画像診断の進歩により，門脈血行動態における門脈大循環短絡の多様性が明らかとなり，また，脳における神経伝達物質および種々の代謝物質の動態などが検討され，肝性脳症の病態解析が進んでいる．さらに，潜在性肝性脳症（意識状態が一見正常と判断される例において定量的精神神経機能検査を行うと少なからず異常を認める例）の概念が提唱され，その診断，病態，臨床的意義について議論されてきている．一方，治療では分岐鎖アミノ酸（BCAA）製剤の位置づけが明確にされ，肝性脳症の改善のみならず蛋白アミノ酸代謝異常の是正やQOLの改善，さらには発癌抑制の可能性も示唆されてきており，新たな展開を迎えている．しかし，高度の肝細胞機能障害をともなう肝硬変例では，今なお治療に難渋することが多く，予後も不良であり，最終的には肝移植を受ける例が増えつつある．

本稿では，とくに肝硬変に起因する肝性脳症の治療について最新の知見を含めて解説する．

Ⅰ　臨床病型

最近，欧米では，新しい肝性脳症の分類(Table 1）が提案されており，肝硬変による肝性脳症はC型として，さらに，エピソード型，持続型，ミニマル肝性脳症（潜在性肝性脳症）に分類している[1)]．この分類では肝性脳症の発症様式や持続期間を重視しており，肝疾患とは異なる原因によって生じる大脳疾患を除外しているが，アンモニア血症をきたす先天性尿素サイクル異常症（高シト

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Table 1. 肝性脳症の新しい分類

型	名称	サブカテゴリー
A（Acute）型	急性肝不全（劇症肝炎など）でみられる脳症	
B（Bypass）型	門脈～大循環系バイパスによる脳症で，肝硬変などの肝疾患をともなわない	
C（Cirrhosis）型	肝硬変と門脈圧亢進症/門脈～大循環短絡路バイパスでみられる脳症	
	エピソード（間欠）型脳症	1. 誘因あり型 2. 誘因なし型 ①再発型（2回以上/年） ②非再発（特発）型
	持続型脳症	1. 軽症型（grade I） 2. 重症型（grade II～IV）
	ミニマル脳症	3. 治療依存型 潜在性脳症といわれたもの

Table 2. 肝硬変による肝性脳症の臨床病型

1. シャント型：
   門脈—大循環短絡（portal-systemic shunt）によりアンモニアなどの中毒性物質が門脈より直接大循環に流入することによる．多くの肝硬変（肝癌合併例も含む），特発性門脈圧亢進症などが該当し，明らかな誘因を認める例が多い．
2. 肝細胞障害型：
   末期昏睡型とも呼ばれる．門脈—大循環短絡を伴うが肝細胞障害因子が強い例．肝硬変のうち高度の黄疸や肝機能異常を伴う例が該当する．誘因不明例が多い．

ルリン血症など）による肝性脳症例の位置づけが明確でなく，サブカテゴリーについてもさらに検討が必要と考えられる．ミニマル肝性脳症は潜在性肝性脳症[2]と同一の病態であり昏睡度ゼロの状態を意味するが，この病態を顕性脳症の前段階の病態と捉えるか否かについてはいまだ議論が分かれている．また，潜在性肝性脳症は知識，数唱，単語といった言語性の認知能は比較的保たれるのに対して，動作性の認知能の低下が特徴とされる．したがって，WAIS知能検査のうち積木試験（block design test），符号試験（digit symbol test），さらには数字追跡試験（number connection test A and B）の3項目を実施し，どれか1項目に異常を認める場合に潜在性肝性脳症と診断することが多い．しかし，診断のための検査法としてのゴールドスタンダードが確立されていないため，その実態（頻度，予後）は報告者によって異なっている[3)~6)]．最近，わが国でもコンピューターを用いた精神神経機能検査法が開発され，罹病率や脳症の顕性化率などが検討されている[7)]．

一方，わが国では肝硬変による肝性脳症を肝細胞障害の強いタイプ（肝細胞障害型あるいは末期昏睡型）と門脈大循環シャント因子が強いタイプ（シャント型あるいは慢性再発型）に分類している（Table 2）．この分類は，肝硬変の病態には肝細胞機能障害と門脈大循環シャントの2つの要因が相互に関連していることを基本とし，治療の反応性や予後を重視したものである[8)9)]．しかし，ミニマル肝性脳症などの位置づけは明確にされておらず，今後，欧米との整合性を図る必要があると考えられる．肝細胞障害型とシャント型における肝病態の特徴として，前者では高度の黄疸と肝予備能の著しい低下を認めるが，一方，後者では比較的肝機能は良好である．アンモニア処理能の低下，尿素合成能の低下および門脈大循環シャントによる血液アンモニア濃度の上昇，Fischer比（BCAA/AAA）の低下あるいはBCAA/Tyr（チロシン）比の低下は両病型とも共通してみられ

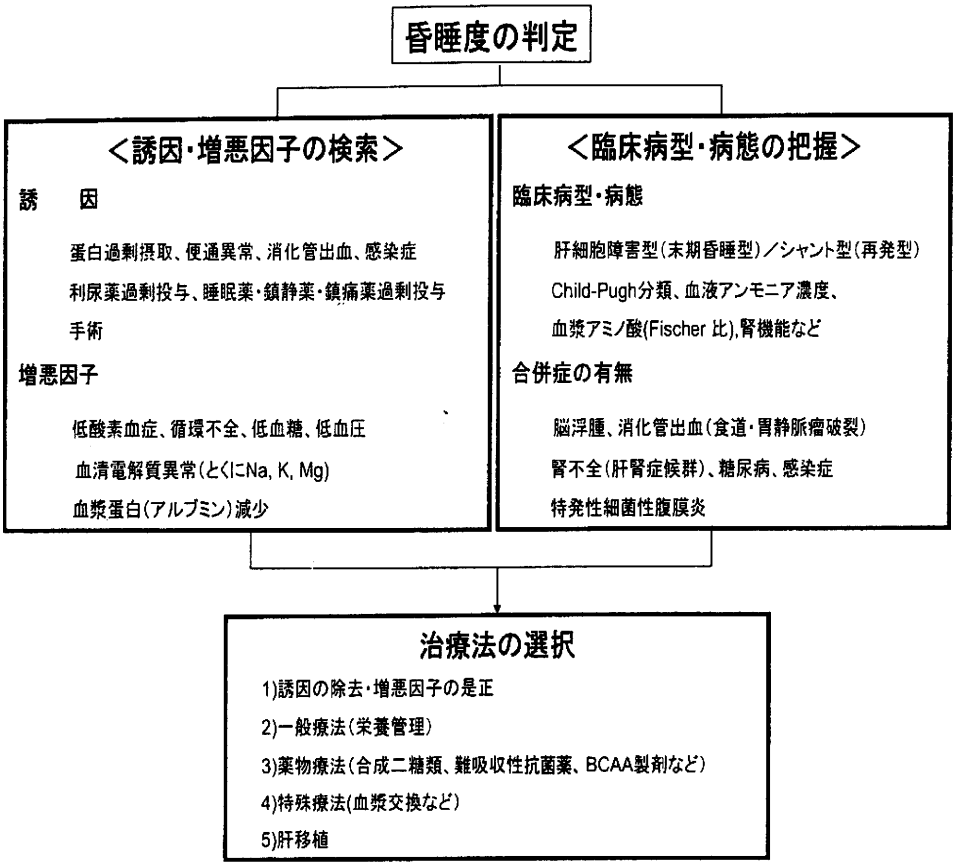

Figure 1. 肝硬変肝性脳症の治療指針

る．なお，先天性尿素サイクル代謝異常症では血液アンモニア濃度の著明な上昇がみられ，それぞれの疾患に応じた特徴的なアミノ酸の変動が観察される．

肝性脳症の重症度は通常昏睡度で表す．わが国では犬山シンポジウムによる昏睡度分類（I～V度）が広く用いられている．欧米ではWest Havenクライテリアとして4段階に分類することが提唱されているが[2]，いずれにしても昏睡I度の判定が難しく，retrospectiveにしか判定できない場合が多い．欧米の分類では昏睡I度の判定としてTMT-Aなどによる評価を提唱している[3]．

II 治 療

肝性脳症の誘因や増悪因子，臨床病型および合併症の有無を把握して，治療方針を決定する（Figure 1）．代表的な誘因として食事蛋白量の過剰摂取，消化管出血，便通異常（とくに便秘），感染症，鎮静剤・鎮痛剤の過剰投与，利尿剤の過剰投与による電解質異常・脱水などがあり，われわれの成績[10]では約70%の例に何らかの誘因を認める．近年は消化管出血による肝性脳症例が減少し，誘因不明例が増加している．肝癌合併例では腹腔内出血も肝性脳症の誘因の1つとなる．また，脳症の増悪因子として低酸素血症，循環不全，低血糖，低血圧，血清電解質異常（とくにナトリウム，カリウム，マグネシウム），血漿蛋白（アルブミン）減少などがある．

治療では，誘因の除去・増悪因子の是正とともに，腸管内の清浄化（アンモニアなどの中毒性物質の産生および吸収を抑制する，腸内細菌によるアンモニアの産生を抑制）を図る対策が基本であり[11]，これに肝細胞機能の改善を図る対策が加わる．肝硬変による肝性脳症の場合，たとえ昏睡IV度またはV度であってもシャント型では短期的には完全意識覚醒が得られることは可能である．しかし，いずれの病型であっても内科的治療による生命予後は必ずしも満足すべきものではない[12]．