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Transcatheter Arterial Chemo-Embolization with a Fine-Powder Formulation of Cisplatin for Unresectable Hepatocellular Carcinoma

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1. Introduction

Hepatocellular carcinoma (HCC) is the cancer with the sixth highest incidence in the world.[1] The incidence of this cancer has increased significantly in the United States, Japan and several European countries over the last two or three decades. HCC as a cause of death is also increasing throughout the world.[2-5] Development of new treatments for HCC has helped to improve patient prognosis.[6, 7] Transcatheter arterial chemoembolization (TACE) is one such treatment, and has been applied to patients with multiple or unresectable HCC.[8, 9] However, HCC has been reported to progress within the short period of multiple sessions of TACE into a complicated condition, even though the treatment is temporarily effective. In recent years, TACE using an emulsion of doxorubicin (ADM) with lipiodol (LPD) (ADM-LPD emulsion) followed by embolization with gelatin sponge has commonly been employed for HCC treatment.[10, 11] However, the tumors have been demonstrated to show a high frequency of recurrence after TACE.[9, 12, 13] Cisplatin (CDDP), a platinum compound, is an effective anticancer agent used in the treatment of various malignancies.[14] Researchers have recently reported that TACE using a suspension of CDDP in LPD may be more effective against unresectable HCC than that using ADM-LPD emulsion.[15, 16] Moreover, a fine-powder formulation of CDDP (DDPH, IA-call; Nipponkayaku, Tokyo, Japan) has also been available since 2004 as a therapeutic agent for intra-arterial infusion in Japan.

In this article, we report the results of a retrospective comparative review of TACE using a suspension of DDPH in LPD (DDPH-LPD suspension) and an emulsion of ADM in LPD, in terms of the response rate (RR), progression-free survival (PFS) and overall survival (OS). Moreover, we analyzed prognostic factors in patients undergoing TACE using DDPH-LPD suspension or ADM-LPD emulsion.

2. Methods

2.1 Patients

We reviewed 468 consecutive HCC patients who had undergone TACE using DDPH or ADM between April 2004 and September 2008 at the Hospital of Iwate Medical

University. HCC was diagnosed based on distinctive findings on ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and angiography, and serum levels of des-γ-carboxy prothrombin (DCP) and α-fetoprotein (AFP). Histological examination was not always applied. Liver function was evaluated according to the Child-Pugh classification.[17] Tumor stage was judged by the TNM classification established by the International Union Against Cancer.[18] The extent of portal vein invasion was classified as follows: Vp0, no invasion of the portal vein; Vp1, invasion of the third or more distal branch of the left or right portal vein; Vp2, 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.

We excluded 18 patients with serum bilirubin levels over 3.0 mg/dL, 12 patients with extra-hepatic metastasis, and 30 patients with uncontrolled ascites. In addition, we excluded 77 patients who had undergone repeated sessions of TACE using different regimens, and 44 patients who showed disease progression and received hepatic arterial infusion chemotherapy (HAIC) and/or systemic chemotherapy as additional therapy.

A final total of 287 HCC patients were enrolled in this study. All of the enrolled patients met the eligibility criteria for inclusion in the analysis described in the next paragraph. Patients were divided into two groups: one group consisting of 120 patients who had undergone TACE using DDPH-LPD suspension (DDPH group); and another group consisting of 167 patients who had undergone TACE using an emulsion of LPD with ADM (ADM group). Of the 120 patients in the DDPH group, 44 had also received various additional therapies such as radiofrequency ablation (RFA) or surgical operation (OPE) after TACE, and 76 patients had undergone TACE alone during the study period. Similarly, 79 patients of the ADM group had received various additional therapies such as RFA or OPE after TACE, and 88 patients had undergone TACE alone without any other therapies during the study period.

Informed consent was obtained from all 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.

2.2 Eligibility criteria

Eligibility criteria for patients in this study were as follows: 1) no evidence of extrahepatic metastasis; 2) no evidence of active heart or renal diseases meeting the contraindications for ADM and CDDP therapy, respectively; 3) Eastern Cooperative Oncology Group (ECOG) performance status (PS)[19] level 0-2; 4) no uncontrolled ascites or pleural effusion; and 5) total serum bilirubin (T-Bil) less than 3 mg/dL. The presence of underlying liver disease such as hepatitis or cirrhosis was confirmed by laboratory, radiological examinations and pathological examinations. We classified chronic hepatitis patients into Child-Pugh class A, because chronic hepatitis is a known pre-cirrhotic condition.

2.3 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, Tokyo, Japan) and then mixed with 3-10 mL of LPD.

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

2.4 Treatment regimen

The patient enrolment period for the DDHP and ADM groups extended from May 2006 to September 2008 and April 2004 to September 2008, respectively. All patients provided fully informed consent prior to TACE. In terms of embolization agents, gelatin sponge particles (Gelpart; Nipponkayaku, Tokyo, Japan) were used for all patients.

After TACE, additional RFA or OPE therapy was provided to patients who met the following inclusion criteria: the presence of up to three tumors with none exceeding 30 mm in diameter or a solitary tumor less than 50 mm in diameter. Regardless of the additional therapy requirement, all patients were followed up with US, CT and/or MRI after 1 month, then every 3 months thereafter. TACE was undertaken again when relapse of treated lesions and/or new hepatic lesions were detected. These patients received additional TACE using the same agent during the follow-up period. TACE or TACE with additional therapy (RFA or OPE) was repeated until complete regression of the tumor was obtained, or until the patient could no longer be treated.

2.5 Post-treatment assessment

Tumor response was assessed by US, CT and/or MRI, conducted 1 month from the start of treatment and every 3 months thereafter. 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.[20-23] By measurement of the two largest perpendicular diameters of the tumor, we classified 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 a decrease of at least 50% in all measurable lesions; progressive disease (PD), an increase in tumor size exceeding 25% of all measurable lesions or appearance of a new lesion; stable disease (SD), disease not qualifying for classification as CR, PR, or PD.

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

2.6 Evaluation of therapeutic effects

We analyzed outcomes in the DDPH and ADM groups in terms of RR, PFS and OS in September 2008. In addition, we also evaluated all patients for survival using uni- and multivariate analyses. Duration of response was calculated from the date of the start of treatment to the date of documented progression. Survival time was calculated from the date of the start of treatment to the date of death or last day of follow-up.

US, CT and/or MRI were performed as mentioned above. In addition, serum levels of biochemical parameters and tumor markers such as AFP and DCP were also measured before and after treatment. The same tests were repeated after completion of every session of treatment.

2.7 Statistical analysis

Differences in background clinical characteristics of patients between the DDPH and ADM groups were assessed using the Mann-Whitney *U* test, logistic regression test, or the χ^2 test, as appropriate.

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

3. Results

3.1 Patient profiles (table 1)

Characteristics of the 287 patients (200 men, 87 women) in both groups are summarized in Table 1. Mean age was 68.4 years (range, 21-90 years).

For the assessment of differences in patient characteristics, patients were divided into two groups based on each characteristic, and significant differences were observed between the DDPH and ADM groups in relation to the gender distribution, TNM classification, tumor size and number of tumors. That is, the DPHH group showed a significantly higher proportion of men ($P=0.030$), higher frequency of more advanced TNM classification ($P<0.001$), and larger tumor size and number ($P=0.004$, $P=0.026$, respectively) than the ADM group. No significant differences in any of the other characteristics were seen between groups.

In relation to differences in the characteristics of patients with no apparent history of additional therapy, significant differences in gender distribution and TNM classification were evident between groups, with higher proportions of men ($P=0.031$) and advanced TNM classification ($P=0.026$) in the DPHH group. No significant differences in any of the other characteristics were seen between groups.

On the other hand, with regard to differences in the characteristics of patients who received additional therapy, the DDPH group differed significantly from the ADM group in terms of TNM classification, tumor size and number of tumors. That is, TNM classification was more advanced ($P=0.003$), tumor size was larger ($P=0.007$) and number of tumors was greater ($P=0.050$) in the DDPH group. No significant differences in other patient characteristics were evident between groups.

	Overall		
Characteristics	**DDPH**	**ADM**	**P value**
No. of patients	120	167	
Age (years) [Median, (range)]	66 (32-87)	69 (21-90)	0.073
Gender (Male / Female)	92/28	108/59	0.030
Etiology (HBV/ HCV / NBNC)	17/83/20	21/119/27	0.911
Child- Pugh (A / B / C)	76/40/4	103/55/8	0.825
TNM classification (I-II / III-IV)	29/91	80/87	< 0.001
Tumor size (≤ 3.0/ >3.0 cm)	44/76	90/77	0.004
Number of tumors (1-3 / ≥4)	68/52	116/51	0.026
PVTT (Vp0-2 / Vp3-4)	106/14	158/9	0.053
Total bilirubin (≤ 1.5 / >1.5 mg/dL)	106/14	150/16	0.581
Albumin (≤ 3.5 / >3.5 g/dL)	54/66	73/93	0.863
AFP (≤ 1000 / >1000 ng/mL)	108/12	155/11	0.301
DCP (≤ 1000 / >1000 mAU/mL)	99/17	146/17	0.288

	According to additional therapy					
	Additional therapy (-)			Additional therapy (+)		
Characteristics	**DDPH**	**ADM**	**P value**	**DDPH**	**ADM**	**P value**
No. of patients	76	88		44	79	
Age (years) [Median, (range)]	67 (32-87)	69 (21-90)	0.093	63 (44-81)	68 (42-80)	0.143
Gender (Male/Female)	57/19	52/36	0.031	35/9	56/23	0.294
Etiology (HBV/HCV/NBNC)	11/50/15	8/64/16	0.508	7/32/5	15/53/11	0.818
Child- Pugh (A/B/C)	47/26/3	45/36/7	0.303	29/14/11	58/19/2	0.598
TNM classification (I-II/III-IV)	10/66	24/64	0.026	19/25	56/23	0.003
Tumor size (≤ 3.0/>3.0 cm)	21/55	30/58	0.373	23/21	60/19	0.007
Number of tumors (1-3/≥4)	35/41	46/42	0.427	33/11	70/9	0.050
PVTT (Vp0-2/Vp3-4)	62/14	80/8	0.080	44/0	78/1	0.454
Total bilirubin (≤ 1.5 / >1.5 mg/dL)	66/10	75/13	0.906	40/4	75/4	0.385
Albumin (≤ 3.5 / >3.5 g/dL)	38/38	45/42	0.822	16/28	28/51	0.919
AFP (≤ 1000 />1000 ng/mL)	68/8	79/8	0.776	40/4	76/3	0.225
DCP(≤ 1000/>1000 mAU/mL)	59/14	73/14	0.609	41/3	73/3	0.468

Table 1. Patient characteristics

Data are expressed as median with range values, or the number of patients. 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. Stages of HCC according to TNM classification were clustered into two groups (I–II and III–IV). Tumor characteristics and other parameters were classified as follows: tumor size, ≤ 3.0 vs. >3.0 cm; tumor number, 1-3 vs. >4; extent of PVTT, Vp0-2 vs. Vp3-4; serum bilirubin, ≤ 1.5 vs. >1.5 mg/dL; serum albumin, ≤ 3.5 vs. >3.5 g/dL; serum AFP levels, ≤ 1000 vs. >1000 ng/mL; and serum DCP levels, ≤ 1000 vs. >1000 mAU/mL.

3.2 Response to therapy (table 2)

3.2.1 Evaluation of the total subject population

RR for all 287 patients was evaluated after one session of therapy. Table 2 shows tumor responses in the two groups. In the DDPH group, 34 (28.3%), 49 (40.8%), 12 (10.0%) and 25 (20.9%) patients showed CR, PR, SD and PD, respectively. In the ADM group, 69 (41.4%), 23 (13.8%), 5 (2.9%) and 70 (41.9%) patients showed CR, PR, SD and PD, respectively. The objective response rate (CR + PR / all cases in each group) was thus significantly higher in the DDPH group (69.1%) than in the ADM group (55.2%; *P*=0.0159).

	Overall		
Response	**DDPH (n=120)**	**ADM (n=167)**	**P value**
CR(%)	34 (28.3%)	69 (41.4%)	
PR(%)	49 (40.8%)	23 (13.8%)	
SD(%)	12 (10.0%)	5 (2.9%)	
PD(%)	25 (20.9%)	70 (41.9%)	
CR+PR(%)	83 (69.1%)	92 (55.2%)	0.016

	Additional therapy					
	(-)			(+)		
Response	**DDPH (n=76)**	**ADM (n=88)**	**P value**	**DDPH (n=44)**	**ADM (n=79)**	**P value**
CR(%)	2 (2.7%)	5 (5.7%)		32 (72.7%)	64 (81.0%)	
PR(%)	39 (51.3%)	16 (18.2%)		10 (22.7%)	7 (8.9%)	
SD(%)	23 (30.2%)	5 (5.7%)		2 (4.6%)	0 (0%)	
PD(%)	12 (15.8%)	62 (70.4%)		0 (0%)	8 (10.1%)	
CR+PR(%)	41 (54.0%)	21 (23.9%)	<0.001	42 (95.4%)	71 (89.9%)	0.278

Table 2. Response

3.2.2 Evaluation of patients who reported no history of additional therapy

In the DDPH group, 2 (2.7%), 39 (51.3%), 23 (30.2%) and 12 (15.8%) patients showed CR, PR, SD and PD, respectively. In the ADM group, 5 (5.7%), 16 (18.2%), 5 (5.7%) and 62 (70.4%) patients showed CR, PR, SD and PD, respectively. The objective response rate was thus significantly higher in the DDPH group (54.0%) than in the ADM group (23.9%; $P<0.0001$).

3.2.3 Evaluation of patients who reported a history of additional therapy

In the DDPH group, 32 (72.7%), 10 (22.7%), 2 (4.6%) and 0 (0%) patients showed CR, PR, SD and PD, respectively. In the ADM group, 64 (81.0%), 7 (8.9%), 0 (0%) and 8 (10.1%) patients showed CR, PR, SD and PD, respectively. No significant difference in objective response rate was apparent between groups, with 95.4% in the DDPH group and 89.9% in the ADM group ($P=0.2778$).

Data are expressed as number of patients and percentages. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

3.3 PFS (fig. 1)

3.3.1 Evaluation of the entire subject population

Median PFS in the DDPH group and ADM group was 11.1 months and 5.0 months, respectively. PFS rates at 6, 12, 18 and 24 months were 70.0%, 47.0%, 27.2% and 24.5%, respectively, in the DDPH group. In contrast, corresponding values were 46.4%, 31.0%, 21.5% and 18.8%, respectively, in the ADM group. PFS rates were significantly higher in the DDPH group than in the ADM group ($P=0.0045$).

3.3.2 Evaluation of patients who reported no history of additional therapy

Median PFS was 7.6 months in the DDPH group and 3.0 months in the ADM group. PFS rates at 6, 12, 18 and 24 months were 56.5%, 32.2%, 15.3% and 15.3%, respectively, in the DDPH group. In contrast, corresponding values were 18.4%, 10.3%, 5.4% and 5.4%, respectively, in the ADM group. PFS rates were significantly higher in the DDPH group than in the ADM group ($P<0.0001$).

3.3.3 Evaluation of patients who reported a history of additional therapy

Median PFS was 17.7 months in the DDPH group and 12.9 months in the ADM group. PFS rates at 6, 12, 18 and 24 months were 90.7%, 74.9%, 42.1% and 42.1%, respectively, in the DDPH group, and 75.9%, 52.6%, 39.3% and 32.3%, respectively, in the ADM group. Although no significant differences in PFS rates were apparent between groups, rates tended to be higher in the DDPH group than in the ADM group ($P=0.1171$).

PFS rate was significantly higher in the DDPH group than in the ADM group in both assessment of the entire study population and assessment of patients who reported no history of receiving additional therapy (log-rank test: $P=0.05$, $P<0.001$, respectively). The difference in PFS rates between patients of the two groups who had received additional therapy was not significant, but a strong tendency was evident (log-rank test: $P=0.117$).

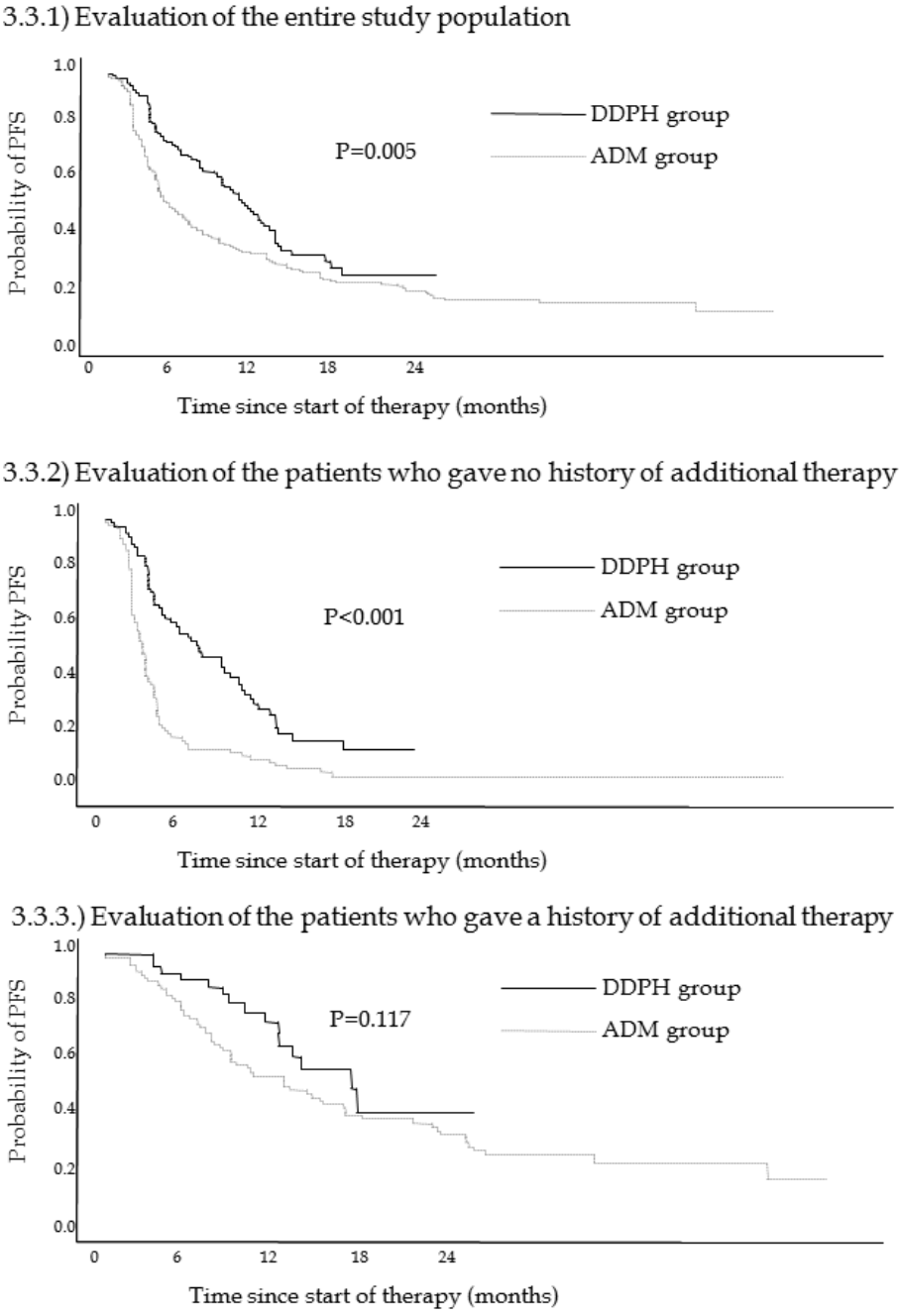

Fig. 1. Comparison of progression-free survival (PFS) rates between DDPH and ADM groups.

3.4 Survival (fig. 2, tables 3, 4)

3.4.1 Evaluation of the entire subject population

Median survival time (MST) in the DDPH and ADM groups was 'not reached' and 45.3 months, respectively. OS at 6, 12, 18, and 24 months were 94.7%, 86.3%, 82.3% and 77.5%, respectively, in the DDPH group. Corresponding values were 94.3%, 82.7%, 74.9% and 69.5%, respectively, in the ADM group. No significant differences in OS were seen between groups (P=0.236).

Univariate analysis to identify predictors of survival indicated seven possible factors affecting survival: Child-Pugh class; TNM classification; tumor size; number of tumors; PVTT; T-Bil; and DCP (Table 3). Multivariate analysis taking all of the factors identified by univariate analysis into account identified treatment regimen, Child-Pugh class, number of tumors, PVTT and DCP as independent factors affecting survival (Table 4).

3.4.2 Evaluation of patients who reported no history of additional therapy

MST in the DDPH and ADM groups was 'not reached' and 20.7 months, respectively. OS at 6, 12, 18, and 24 months were 91.6%, 78.9%, 73.4% and 67.3%, respectively, in the DDPH group. Corresponding values in the ADM group were 87.3%, 68.3%, 54.8% and 46.4%, respectively. OS was significantly higher in the DDPH group than in the ADM group (P=0.046).

3.4.3 Evaluation of patients who reported a history of additional therapy

MST in both groups was 'not reached'. OS at 6, 12, 18 and 24 months were 100%, 100%, 100% and 100%, respectively, in the DDPH group, compared to 100%, 95.9%, 94.5% and 90.1%, respectively, in the ADM group. No significant differences in OS were evident between groups (P=0.456).

OS was significantly higher in the DDPH group than in the ADM group in the assessment of the entire study population, as well as among patients who reported no history of receiving additional therapy (log-rank test: P=0.046). No significant difference in OS was seen between patients in the two groups who had received additional therapy (log-rank test: P=0.236, P=0.456, respectively).

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.

3.5 Adverse effects (table 5)

Table 5 shows a summary of adverse effects in the two groups. Abdominal pain, nausea/vomiting, fever, and elevation of serum transaminase levels were observed in most patients of both groups, but these symptoms were mild and transient. The frequency of nausea/ vomiting was significantly higher in the DDPH group than in the ADM group (P<0.0001). In addition, frequencies of occlusion of the hepatic artery and leucopenia were significantly higher in the ADM group than in the DDPH group (P<0.001 and P=0.002, respectively). No other serious complications or treatment-related deaths were observed in either group.

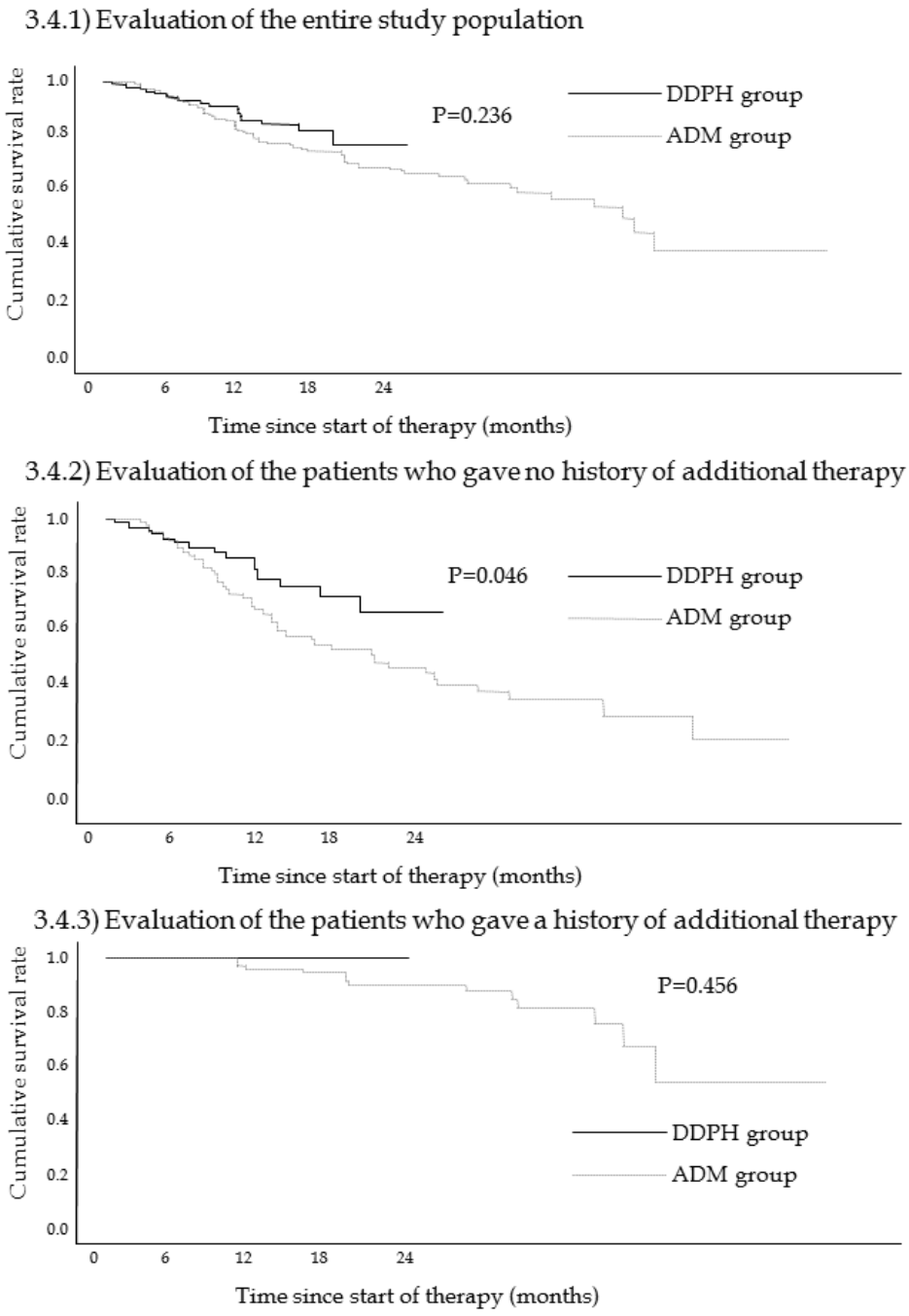

Fig. 2. Comparison of OS between DDPH and ADM groups.

Variable	Hazard ratio	95% confidence interval	P value
Treatment regimen (ADM vs. DDPH)	0.752	0.425-1.330	0.327
Age (≤65 years vs. >65 years)	1.466	0.895-2.400	0.129
Gender (Female vs. Male)	1.116	0.681-1.828	0.663
Etiology (NBNC vs. HBV/ HCV)	0.960	0.587-1.572	0.872
Child Pugh classification (A vs. B/C)	1.747	0.105-2.762	0.017
TNM classification (I-II vs. III-IV)	3.567	2.037-6.244	< 0.001
Tumor size (≤ 3.0 vs. >3.0 cm)	2.871	1.754-4.701	< 0.001
Number of tumors (1-3 vs. ≥4)	4.073	2.550-6.503	< 0.001
PVTT (Vp0-2 vs. Vp3-4)	6.951	3.804-12.703	< 0.001
Total bilirubin (≤ 1.5 vs. >1.5 mg/dL)	2.512	1.347-4.684	0.004
Albumin (≤ 3.5 vs. >3.5 g/dL)	0.633	0.400-1.002	0.051
AFP (≤ 1000 vs. >1000 ng/mL)	1.882	0.860-4.117	0.113
DCP (≤ 1000 vs. >1000 mAU/mL)	3.266	1.884-5.786	< 0.001

Table 3. Univariate analysis for identifying predictors of survival

Variable	Hazard ratio	95% confidence interval	P value
Treatment regimen (ADM vs. DDPH)	0.428	0.196-0.934	0.033
Child Pugh classification (A vs. B/C)	3.102	1.685-5.712	0.001
Number of tumors (1-3 vs. ≥4)	5.831	3.041-11.181	<0.001
PVTT (Vp0-2 vs. Vp3-4)	5.428	2.197-13.409	0.001
DCP (≤ 1000 vs. >1000 mAU/mL)	3.890	1.747-8.663	0.001

PVTT, portal vein tumor thrombosis; DCP, des-γ-carboxy prothrombin

Table 4. Multivariate analysis for identifying predictors of survival

Adverse effect	Treatment group		P value
	DDPH group (n=120)	ADM group (n=167)	
Nausea / Vomiting	101 (84.2%)	103 (61.6%)	<0.001
Fever	96 (80.0%)	138 (82.6%)	0.571
Abdominal pain	83 (69.1%)	116 (69.4%)	0.957
Elevation of trans-aminase levels	87 (72.5%)	121 (72.4%)	0.993
Liver abscess	1 (0.8%)	2 (1.2%)	0.765
Hepatic artery occlusion	1 (0.8%)	28 (16.7%)	<0.001
Renal or liver failure	0 (0.0%)	2 (1.2%)	0.229
Leucopenia	5 (4.2%)	26 (15.6%)	0.002
Thrombocytopenia	7 (5.8%)	12 (7.2%)	0.650
Fatigue	38 (31.6%)	51 (30.5%)	0.839

Table 5. Adverse events

Data are expressed as number of patients, with percentages indicated in parentheses.

4. Discussion

TACE has been widely used for the treatment of unresectable HCC.[8, 9] The most commonly used agent in TACE for HCC treatment is an emulsion of LPD and ADM, followed by embolization with gelatin sponge particles,[10, 11] but tumors frequently recur[9, 12, 13] or residual tumors are observed at a high rate. CDDP is an effective anticancer agent used in the treatment of various malignancies.[14] Ono et al.[15] reported that TACE using a suspension of CDDP powder in LPD was more effective against unresectable HCC than that using an emulsion of ADM and LPD. Other investigators have also frequently reported favorable results obtained with TACE using a suspension of CDDP powder in LPD in HCC patients.[16, 24] However, the CDDP powder for this therapy was difficult to produce because of the characteristics of the drug formulation. CDDP powder thus had to be custom-made in individual institutions.[25] Consequently, when an institution was able to dispense CDDP powder in their own pharmacy department, TACE using a suspension of CDDP powder in LPD was undertaken.

A fine-powder formulation of CDDP, "DDPH", has been available for intra-arterial infusion 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. The DDPH-LPD suspension for TACE in HCC patients was expected to yield better therapeutic outcomes, so TACE using DDPH has become widespread in Japanese institutions. Nevertheless, the efficacy of TACE using DDPH-LPD suspension has not yet been reported. We therefore compared the outcomes of TACE using DDPH-LPD suspension and an emulsion of LPD with ADM.

The antitumor activity of CDDP is closely associated with the serum concentration of the drug.[26] Antitumor activity can thus be enhanced by increasing the dose. LPD acts as a selective carrier of anticancer agents and as an embolic material;[20] 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, this approach is nonetheless used to achieve a targeted drug delivery system with long-lasting accumulation in the tumor and gradual drug release. Augmented antitumor efficacy and milder side-effects have therefore come to be expected with the use of this substance for TACE. In fact, Morimoto et al.[27] investigated the pharmacological advantages of TACE using DDPH for hypervascular hepatic tumors in animal experiments. They reported that the tumor concentration of 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 plasma concentrations of the platinum agent at 5 and 10 min from start of infusion were lower in the DDPH-LPD-TACE group than in the DDPH-HAI group. Based on those findings, we decided to perform TACE using DDPH-LPD suspension.

Analysis of the results for the entire study population revealed that the objective response rate was significantly higher in the DDPH group than in the ADM group. Moreover, while no significant difference in OS was seen between groups, the OS of patients who had not received any additional therapy in the DDPH group was significantly higher than that of patients with no history of additional therapy in the ADM group. This could be explained as being due to the fact that TACE with ADM cannot be repeated as required, given the high

frequency of adverse effects of ADM such as leucopenia, severe vascular changes and occlusion of the hepatic artery.[15, 28, 29] In fact, the incidences of leucopenia and occlusion of the hepatic artery were significantly higher in the ADM group in our study than in the DDPH group. Second, we concluded that anthracyclines such as ADM may be relatively less effective against HCC; this is attributable to high expression levels of P-glycoprotein, which transports antitumor agents such as anthracyclines and vinca alkaloids from cells with a highly active efflux mechanism in HCC tumors.[30]

On the other hand, Pelletier et al.[31] reported that TACE with CDDP sometimes caused severe complications, such as acute hepatic failure, without providing any significant improvement in survival rate. Severe complications could be expected with the high doses of CDDP used in that study. Modification of the CDDP dose used for the treatment to 50 mg of DDHP in our study resulted in lower severity of complications.

In terms of our results, no significant differences in objective response rate or OS were identified between DDPH and ADM groups in patients who reported a history of previous additional therapy. However, considering that the observation period for the DDPH group was shorter than that for the ADM group and that PFS tended to be longer in the DDPH group as compared with that in the ADM group, a significant difference in OS may be observed if the DDPH group was followed up for a longer period.

To avoid the confounding effects of any deviations in patient characteristics causing an impact on the results, such as the gender distribution, TNM classification, or larger size or number of tumors, we used multivariate analysis to compare efficacy between regimens. This analysis identified the treatment regimen employed for TACE as one of the most important prognostic factors.

5. Conclusion

We conclude that TACE using DDPH-LPD suspension could provide a useful treatment strategy for HCC patients, although further studies are required for a more thorough evaluation of the effectiveness of this therapy.

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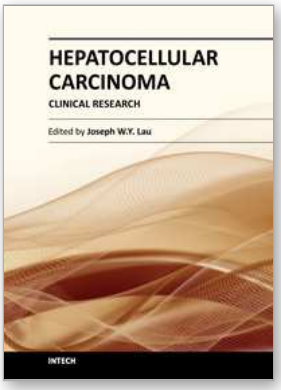

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This book covers the clinical aspects of hepatocellular carcinoma. This book is a compendium of papers written by experts from different parts of the world to present the most up-to-date knowledge on the clinical aspects of hepatocellular carcinoma. This book is divided into three sections: (I) Diagnosis / Differential Diagnosis; (II) Surgical Treatment; (III) Non-surgical Treatment. There are 19 chapters covering topics from novel diagnostic methods to hepatic lesions mimicking hepatocellular carcinoma, from laparoscopic liver resection to major hepatectomy without allogeneic blood transfusion, from molecular targeted therapy to transarterial radioembolization, and from local ablative therapy to regional therapy. This volume is an important contribution to the clinical management of patients with hepatocellular carcinoma. The intended readers of this book are clinicians who are interested in hepatocellular carcinoma, including hepatologists, liver surgeons, interventional and diagnostic radiologists, pathologists and epidemiologists. General surgeons, general physicians, trainees, hospital administrators, and instruments and drug manufacturers will also find this book useful as a reference.

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